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Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

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BY
ANN LYKKEGAARD SØRENSEN

DISSERTATION SUBMITTED 2017

AALBORG UNIVERSITY
DENMARK

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Dissertation submitted 2017

Dissertation submitted: 08-08-2017

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ISSN (online): 2246-1302
ISBN (online): 978-87-7210-033-3

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2017

CV

My name is Ann Lykkegaard Sørensen, and this CV presents my professional background and the journey which led to the completion of my PhD study. I became a registered nurse from The Aalborg School of Nursing in 2000 and went on to work with medical, surgical, and psychiatric patients. In 2006, I enrolled at Aarhus University and obtained a Master's degree in Health Science (MHSc) in 2010. Upon completing my Master's degree, I became a lecturer at University College of North Jutland, and I am still there today.

My Master's thesis and other projects were concerned with patient - and medication safety, which specifically spurred my interest in medication safety and my awareness of potentially inappropriate prescribing in psychiatric nursing. I enrolled as a PhD student February 1, 2012, at the Department of Health Sciences and Technology, Aalborg University.

My research has been aimed at medication safety in the field of psychiatry. I used systematic medication reviews performed by clinical pharmacologists, to investigate the characteristics of potentially inappropriate prescribing, and investigate the role of psychiatric nurses in improving medication safety by systematically utilising their observations about medication and patients.

ENGLISH SUMMARY

Medication errors are the most frequent adverse incidents in healthcare systems across the world causing increased mortality, morbidity, and increased costs for both society and patients. Potentially inappropriate prescriptions (PIPs) also lead to increased mortality, morbidity, and increased health care costs. However, PIPs are primarily studied in the elderly. The exclusion of psychiatric patients is common to these studies of medication errors and PIPs. Hence, the aim of this PhD thesis was to investigate the prevalence and potentially clinical consequences of medication errors and PIPs, as well as nurses' ability to identify PIPs for psychiatric patients validated by comparing with the findings of senior clinical pharmacology physicians' (SCPP) medication reviews. Finally, the aim was also to discover nurses' perceptions of nurse-physician collaboration (NPC) on medication optimisation.

The four studies were comprised of two cross-sectional studies, one controlled before-and-after study including psychiactric patients admitted to bed units in the North Denmark Region, and one qualitative thematic study. In Study I, three methods were applied to collect data (observation, unannounced visits, and chart audit), for the purpose of identifying errors in the medication process. The results of Study I showed errors in 17% of all opportunities for error and 8% of errors in the medication were assessed to be potentially harmful and were thus being medication errors. In the next cross-sectional study, Study II, systematic medication reviews were applied by SCPPs to identify PIPs and to assess potential clinical consequences. The study included all psychiatric patients admitted to a bed unit in the North Denmark Region over a three-month period. The results in Study II demonstrated 349 PIPs in 1291 prescriptions with 33% of patients affected by at least one potentially serious prescription and 12% of patients affected by at least one potentially fatal prescription. Study III, was a controlled before-and-after study, with a two-month baseline and a six-month follow-up period, where all patients received a medication review by SCPPs and these medication reviews were considered gold standard. The intervention consisted of a pharmacology training course for nurses in the intervention bed units and afterwards the nurses reviewed medication lists to identify PIPs. The study was carried out in two intervention bed units and two control bed units. Primary outcomes were the SCPPs identification of PIPs, before and during the intervention, but adjusted for the nurses' identifications of PIPs during the intervention. Results indicated potential improvement in the mean number of PIPs per patient and the number of patients with at least one PIP. Secondary outcomes counted the prevalence and types of PIPs altered by physicians as a consequence of nurses observations. Study IV, the final study, was a qualitative thematic analysis of the nurses' perceptions of NPC on medication optimisation for

psychiatric patients. The nurses described challenges with NPC relating to both individual as well as organisational factors.

Conclusively, this PhD thesis demonstrates that errors, medication errors and PIPs are frequent in psychiatric patients. Nurses reviewing patients' medications could only produce non-significant potential improvements. These results should be viewed in the light of the fact that the nurses described a perceived everyday work environment, in which beneficial NPC regarding medication optimisation was not given due consideration. Future studies should, on a larger scale, focus on how and by which methods nurses may contribute to better observation, identification, and reporting of errors and the inappropriate use of medication in psychiatry.

DANSK RESUME

Globalt set er medicineringsfejl på hospitaler den hyppigste utilsigtede hændelse og årsag til øget mortalitet, morbiditet og ekstra omkostninger for både samfund og patienter. Potentielt uhensigtsmæssige ordinationer (potentially inappropriate prescriptions (engelsk:PIP)) har også vist sig at medføre øget mortalitet, morbiditet og ekstra omkostninger, men er primært undersøgt for ældre patienter. Fælles for studier af medicineringsfejl og PIPs er, at psykiatriske patienter kun sjældent har været inkluderet. Formålet med denne afhandling var at undersøge prævalens og potentielle, kliniske konsekvenser af medicineringsfejl og PIPs, samt sygeplejerskers evne til at identificere PIPs hos psykiatriske patienter valideret ved sammenligning med kliniske farmakologers medicingennemgang. Endelig var det også formålet at afdække sygeplejerskers oplevelser af samarbejdet med læger om at sikre den bedst mulige medicinske behandling af patienter.

Studierne består af to tværsnitsstudier, et kontrolleret før-og-efter studie samt et kvalitativt tematisk studie. I studie I blev data indsamlet på tre sengeafsnit ved hjælp af tre metoder (observation, kontrolbesøg samt journalaudit), med henblik på identifikation af fejl i medicineringsprocessen. Disse fejl blev vurderet af kliniske farmakologer for potentiel klinisk alvorlighed. Resultaterne viste at der var fejl i 17% af alle muligheder for fejl og at 8% af fejlene i medicineringsprocessen blev vurderet som potentielt skadelige og dermed medicineringsfejl. Efterfølgende blev der udført yderligere et tværsnitsstudie, studie II, hvor kliniske farmakologer ved hjælp af systematisk medicingennemgang identificerede potentielt uhensigtsmæssige ordinationer samt vurderede disse for potentiel klinisk alvorlighed. Studiet fandt sted over en tre måneders periode og inkluderede alle patienter indlagt på et psykiatrisk sengeafsnit i Region Nordjylland. Resultaterne i studie II viste 349 PIPs i 1291 ordinationer samt at 33% af patienterne havde mindst 1 potentielt alvorlig uhensigtsmæssig ordination og 12% af patienterne havde mindst en potentielt fatal uhensigtsmæssig ordination. Studie III, et kontrolleret før-og-efter studie, blev udført på fire psykiatriske sengeafsnit (to interventions afsnit og to kontrol afsnit) over en otte måneders periode. De kliniske farmakologer udførte medicingennemgang for alle inkluderede patienter i studiet og betragtedes som gold standard. Interventionen bestod af et farmakologikursus for sygeplejerskerne på interventionssengeafsnittene. I interventionsperioden gennemgik sygeplejerskerne patienternes medicinlister efter indlæggelse med henblik på at identificere PIPs. Primære effektmål var de kliniske farmakologers identifikation af PIPs, før og under interventionen, men justeret for sygeplejerskernes identifikationer af PIPs under interventionen. Resultaterne indikerede potential forbedring i det gennemsnitlige antal PIPs per patient samt proportionen af patienter med mindst 1 PIP. Sekundære effektmål var prævalens og type af PIPs hvor læger ændrede ordinationer som konsekvens af sygeplejerskernes observationer. Sidste studie, studie IV, var en kvalitativ, tematisk analyse af

sygeplejerskernes opfattelse af samarbejdet med læger om at sikre den bedst mulige medicinske behandling af psykiatriske patienter. Sygeplejerskerne beskrev en række udfordringer i sygeplejerske-læge samarbejdet som relaterede sig både til individuelle såvel som organisatoriske forhold.

Samlet viser denne ph.d., at fejl, medicineringsfejl og potentielt uhensigtsmæssige ordinationer er hyppigt forekommende hos psykiatriske patienter. Det var kun muligt at vise ikke-signifikante potentielle forbedringer ved hjælp af sygeplejerskers gennemgang af medicin. Dette resultat skal ses i lyset af, at interventionen blev gennemført af sygeplejersker, der gav udtryk for en hverdag, hvor hensynet til et godt sygeplejerske-læge samarbejde omkring medicin optimering var begrænset. Fremtidige studier bør i større målestok fokusere på, hvordan og med hvilke metoder sygeplejersker kan bidrage til bedre observation, identifikation og rapportering af fejl og uhensigtsmæssig anvendelse af medicin i psykiatrien.

ACKNOWLEDGEMENTS

This thesis is based on work carried out during my affiliation with the Danish Center of Healthcare Improvements at Aalborg University. I would like to thank the University College of Northern Denmark, and the Danish Center for Healthcare Improvements, Aalborg University, for providing the necessary funding. Without these institutions, the project would not be a reality.

I would also like to thank my main supervisor, Professor and Medical Director Jan Mainz, who encouraged me to engage in research in the fields of quality improvement, psychiatry, and medication safety. I will always remember that it was you who initially provided me with the opportunity for pursuing the challenge of learning to become a researcher. Your knowledge and experience were invaluable.

I want to thank my co-supervisors. Firstly, Marianne Lisby, thank you for always being there and for offering brilliant, rapid feedback, constructive critique and (when necessary) blunt academic honesty. Secondly, Lars Peter Nielsen; your hard work and dedication to my project have been nothing short of amazing, and I am forever indebted. I also need to thank Birgitte Klindt Poulsen. You too have been supportive and extremely giving with your time and knowledge. Thank you, both - for letting me have the privilege of standing on your shoulders.

A heartfelt thank you goes out to all the nurses (wards S1 and S7) who helped with the project and provided a large proportion of the data needed. Thank you to the rest of the staff who kept an open mind and a special thank you to those nurses who proved that 'when the going gets tough, the tough get going' – you know who you are!

I have spent my time in DCHI with amazing colleagues. Thank you for creating an environment where the endeavours towards academic excellence fortunately often interchanged with good laughs! Thank you to Ina Svendsen and Nancy Raakjær for not giving up on me. A special thank you to my office buddy, Flemming Witt Udsen for support on difficult days and Louise Hansen for backup given in so many forms. Finally, Cathrine Elgaard Jensen: even if rain or spears fall, we will do it. For all the days, evenings and weekends – thank you!

This ends where it all began; with my family. Michael, thank you for the love, encouragement, and loyalty you have shown me over the years and thank you for, despite my faults, still being there when I come home. Without you, Dicte, and Helene, I could not have done it. To my mother: Thank you for all the times you solved the impossible equations by stepping in with cooking and taking care of our children. This is also your accomplishment.

LIST OF ABBREVIATIONS

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AR	Adverse Reaction
ATC	Anatomic Therapeutic Chemical (ATC) Classification System
COREQ	Consolidated Criteria for Reporting Qualitative studies
CPOE	Computerized Physician Order Entry
EMA	European Medicines Agency
EMR	Electronic Medical Record
MDD	Major Depressive Disorder
ME	Medication Error
NPC	Nurse-Physician Collaboration
PANSS	Positive and Negative Syndrome Scale
PIP	Potentially Inappropriate Prescription
PRN	Pro Re Nata (medication as needed)
RR	Relative Risk
SCPP	Senior Clinical Pharmacology Physician
TDM	Therapeutic Drug Monitoring
95%CI	95% Confidence Intervals

LIST OF PUBLICATIONS

Paper I The medication process in a psychiatric hospital: are errors a potential threat to patient safety?

Ann Lykkegaard Soerensen, Marianne Lisby, Lars Peter Nielsen, Birgitte Klindt Poulsen, Jan Mainz.

Risk Manag Healthc Policy. 2013;6:23-31.

Paper II Potentially inappropriate prescriptions in patients admitted to a psychiatric hospital.

Ann Lykkegaard Soerensen, Lars Peter Nielsen, Birgitte Klindt Poulsen, Marianne Lisby, Jan Mainz.

Nord J Psychiatry. 2016;70(15):365-73

Paper III Improving medication safety in psychiatry – a controlled intervention study of nurse involvement in avoidance of potentially inappropriate prescriptions

Ann Lykkegaard Sørensen, Marianne Lisby, Lars Peter Nielsen, Birgitte Klindt Poulsen, Jan Mainz.

(Manuscript)

Paper IV Nurses' perceptions of collaborating with physicians about medication optimisation for psychiatric patients.

Ann Lykkegaard Soerensen, Marianne Lisby, Lars Peter Nielsen, Birgitte Klindt Poulsen, Jan Mainz.

(In preparation)

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'Let whoever is in charge keep this simple question in her head (not, how can I always do this right thing myself, but) how can I provide for this right thing to be always done?'
Florence Nightingale

CHAPTER 1. BACKGROUND

1.1. RESEARCH IN MEDICATION SAFETY

Medical errors pose a major threat to patient safety worldwide, and medication errors (MEs) form the largest category of medical errors causing increased mortality, morbidity and costs to society as confirmed by meta-analyses, systematic reviews and individual studies (1–6). Iatrogenic injury had been demonstrated as a massive problem in the early 1990s and called for both public and professional attention (7–10). However, before the millennium change, these large studies of patient injury had little impact on the political agenda until in 2000, patient safety issues were raised with the launch of the Institute of Medicine report “To err is human” (11,12). This report claimed that as many as 98,000 patients die annually as a result of medical errors (11). Worldwide, this statement sparked tremendous activity in patient safety research and projects (13,14).

Psychiatric patients were systematically excluded in the high-impact studies in general medical settings on which the IOM based their recommendations, and thus little evidence on the incidence, types, and causes of error in psychiatric treatment is available (15). Most studies within the field of medication safety have focused exclusively on somatic hospital settings; consequently, there is little research on medication errors and adverse drug events in psychiatry (12,16). However, research has demonstrated that psychiatric in-patients do experience potential and actual harm from adverse drug events (ADEs) (17).

Additionally, there is only a limited body of research on potentially inappropriate prescriptions (PIPs) in psychiatry. Most of the existing research examines specific prescribing practices (18,19) or the inappropriate use of psychoactive drugs in other settings other than mental health (20,21). Attempts to improve the quality of prescribing have been assessed, singling out as the most successful methods audit-feedback interventions and educational out-reach visits involving physicians and pharmacists (22). Despite the medication process being a multidisciplinary activity, very few attempts have been made to involve nurses’ observations in improving the quality of prescribing (23,24) and even less so in mental health settings.

Consequently, it is reasonable to question the safety of the medication process and appropriateness of prescribing in mental health settings as well as to explore interventions and contexts which place nurses centrally in identifying and reporting PIPs.

1.2. THE CONTEXT OF POTENTIALLY INAPPROPRIATE PRESCRIPTIONS AND ERRORS IN THE MEDICATION PROCESS

To describe PIPs and errors in the medication process, I relied on work by Dean, Barber, and Schachter, Aronson and Ferner, and Lisby et al. (25–31). This section describes major points in the works of the authors mentioned above, relating to definitions and classifications of MEs in the context of PIPs.

1.2.1. PRESCRIPTION ERRORS AND CLINICAL DECISION-MAKING

Dean et al. distinguished between 'errors in decision-making' and 'errors in prescription writing' in their practitioner-led definition of a prescribing error achieved through a Delphi process (25). In defining prescribing errors, some respondents objected to including 'errors in decision-making', because a prescription error could be considered part of 'clinical decision-making' rather than 'prescribing'. However, both types of error remained in the final definition:

'A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant 1) reduction in the probability of treatment being timely and effective or 2) increase in the risk of harm when compared with generally accepted practice.' (25)

Thus, when applying the above definition, it is important to acknowledge the bisection. Dean et al. do not bring the term 'inappropriate prescriptions' into play but, by linking prescription errors to clinical decision-making imply that the writing of a prescription is influenced by the available evidence, the individual physician's knowledge and experience as well as patient preferences which provide opportunities for more or less appropriate decisions.

1.2.2. PRESCRIPTION ERRORS, PRESCRIBING FAULTS, AND BALANCED PRESCRIBING

Robin E. Ferner co-authored a study with Sarah E. McDowell and Harriet S. Ferner in which the forms of error were discussed and, inspired by Kirwan (32), errors were described as a disorder of an intentional act which can be divided in two: formulating the plan for action, and executing of the plan (33). This duality of error is essential in understanding errors in the medication process. Aronson and Ferner originally suggested the following definition of MEs*:*

'…a failure in the drug treatment process that leads to or has the potential to lead to, harm to the patient.' (29)

Later the definition of an ME was adopted by European Medicines Agency (EMA) with the addition of 'unintended':

'…an unintended failure in the treatment process that leads to or has the potential to lead to, harm to the patient' (34)

Aronson distinguishes between 'prescribing faults' and 'prescription errors' (27) arising from the ambiguity in the meanings 'prescribing' and 'prescription'. Comparing to the definition by Dean et al., 'prescribing fault' then means a '[wrong] prescribing decision' and 'prescription error' means an '[erroneous] prescription writing process'. Aronson mentions several types of prescribing faults: irrational prescribing, inappropriate prescribing, underprescribing, overprescribing, and ineffective prescribing and refers to this as 'a class of errors' (28). He suggests, however, that due to the substantial overlap between these types of faults, it is helpful to describe them by a definition of their opposite; balanced prescribing. Balanced prescribing is defined as:

'…a process that recommends a medicine appropriate to the patient's condition and, within the limits created by the uncertainty that attends therapeutic decisions, a dosage regimen that optimizes the balance of benefit to harm.' (28)

In the scope of Anderson's work, inappropriate prescribing is a subclass of prescribing faults.

1.2.3. DEFINING MEDICATION ERRORS

Lisby et al. developed and tested a definition of medication errors after reviewing 45 studies presenting with a definition of a medication error (30,31), as follows:

'…an error in the stages of the medication process – ordering, dispensing, administering, and monitoring the effect – causing harm or implying a risk of harming the patient.'

This definition had evolved through a Delphi process involving 13 Danish health organisations and thus represented the most acceptable definition to the participants (31). The definitions by Aronson and Ferner, and Lisby have obvious similarities as both point to harm, or the probability of harm, to the patient. However, the definition by Lisby et al. applies the term 'an error in the stages of the medication process' which is circular reasoning according to Aronson's thoughts on definitions and classification (26). Aronson uses this example:

'…nor do as Dr. Johnson did in his 1755 dictionary and unhelpfully define a hind as 'she to a stag' and a stag as 'the male of the hind'.' (26)

During their Delphi process, Lisby et al. received much protest against the word 'failure', which appears to be used by Aronson and Ferner merely to avoid circularity and signifies 'fallen below some attainable standard' (29). This was not the association expressed by the Danish clinical experts who rejected the term 'failure' as being imprecise and value-laden (31). It is likely, that in a Danish context, using the word 'failure' will be perceived as the individual 'being a failure' which is more shameful than 'having made an error'. In the Delphi process led by Lisby et al., the clinical experts also approved a comprehensive list of error types, including prescription errors divided into the decision-making stage and communicating (writing) stage (31). The understanding of errors in the prescribing stage as being errors in clinical decision-making, or in the writing of a prescription, is also found with Lisby et al. According to Dean et al., an error in decision-making implies that the writing of a prescription is influenced by the available evidence, the individual physicians' knowledge and experience as well as patient preferences which provide opportunities for more or less appropriate decisions.

1.2.4. OPERATIONAL DEFINITIONS

This subsection describes how 'errors', 'MEs', and 'PIPs' are defined in this thesis and its ancillary articles. In this thesis, error is to be understood as 'a planned action which failed to achieve the desired consequences' (35). However, when investigating prescription errors, it is beneficial to consider an error as an intentional act which can be considered in terms of the formulating of a plan or the actual execution of the plan (33). Medication errors are defined as errors in the stages of the medication process – ordering, dispensing, administering, and monitoring the effect – causing harm or implying a risk of harming the patient (31). Likewise, using the definition by Lisby et al., errors are categorised in types, which are described in Appendix A. Intentionality by the physician would be the crux of the matter between error and rule violation and seen in conjunction with the prescribing of medications, means that it appears relatively straightforward whether or not an error is present in the communicating of a prescription. It appears less straightforward as to whether an error is present in the decision-making stage as several factors influence the decisions made. The physician will rely on evidence, clinical experience, and viewpoints which may vary, together with the patient's preferences and individual circumstances. An example to illustrate this concerns off-label prescribing in psychiatry. Off-label prescribing may take different forms, but one approach is to prescribe a dose higher than that recommended by, for example, the European Public Assessment Report. This is an intended (and possibly good) decision to make a rule violation, but not necessarily an error (although it might be). Whatever the case, error, or rule violation, the prescriber has increased the probability of the prescription being inappropriate. In this thesis, the term PIP is

defined as prescribing that introduces a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for the same condition. Additionally, PIP includes the use of drug combinations with known drug–drug interactions, drug–disease interactions, overdosing, use of drugs for a longer time than clinically indicated, as well as the omission of prescribing drugs that are clinically indicated (36,37).

Given the uncertainty surrounding prescribing in psychiatry, the term PIP allows for medications involving risk but possibly also benefit. In this thesis and its ancillary articles, a PIP, regardless of whether it involves an error or a rule violation (‘good’ or ‘bad’), is categorised in types adapted from the work of Lisby et al.

1.3. THE EPISTEMOLOGY OF MEDICATION ERRORS

Researchers have suggested that <1% of all errors in the medication process actually cause harm to the patient (38). This indicates a need to discriminate between important and not-important errors in the medication process; in other words what can harm or not harm patients. The rationale for the given definition of an ME in this thesis was the distinction between harmful and harmless to the patient. It has been suggested that interventions focused on MEs with the potential for harming the patient might also bear the highest positive clinical impact (31,39–41). This raises questions about the definition of MEs and, additionally, what constitutes an error in the medication process. The definitions used in studies of medication safety and iatrogenic harm are diverse, and even though attempts have been made to clarify terminology as well as methodology, there is still variation in the definitions presented in the literature (26,30,42). Several scholars have argued that this lack of consistency may cause difficulties in producing reliable estimates of patient safety; for instance MEs and ADEs (30,43–45).

The methodology used in the large epidemiological studies of ADEs and MEs (9,46,47) could, in all likelihood, be transferred to psychiatric settings, although certain aspects of psychiatric care have to be considered. The main goal in research on ADEs and MEs is to reduce the risk of patients experiencing harm due to medication use and to do so there is a need to establish epidemiological measures regarding the frequency, classification of events and any associations with other variables offering preventability (48,49). These epidemiological measures can be categorised under three headings: identification, classification, and risk factors, which will be clarified in the following sections. These sections also touch on complicating factors related to the psychiatric context.

1.3.1. IDENTIFYING MEDICATION ERRORS

Identification of MEs is essential to improve medication safety, but the methods to do so all have their advantages and problems (49,50). Key approaches to the detection of MEs are voluntary reporting, retrospective chart reviews, computerised monitoring, and searching claims data (48–52). Direct observation of patient care has, however, been identified as a superior yet costly method (51).

Voluntary incident reporting has been a pivotal part of safety initiatives in other fields with the aviation industry leading the way (53,54), and has been adopted by most healthcare institutions as the preferred method for detecting MEs and ADEs (49). However, this method is less sensitive in detecting ADEs and MEs than any other method (51).

Retrospective chart review has proven to be well-suited for identifying ADEs, although not as effectively as direct observation of patient care. This method is also costly and time-consuming and requires that medical personnel correctly register any events that have taken place (51). Also, the reviewers' assessments may display significant variance in identifying, for instance, ADEs (51).

Computerised monitoring is a programme consisting of rules which are applied to, for instance, electronic medical records (EMRs) and indicate the possibility of an ADE being present (55). Studies have successfully demonstrated computerised monitoring as a method of detecting ADEs (56,57). However, positive predictive values still need improvement as computerised monitors frequently alert to false positive ADEs (55).

Medication errors are, in this thesis and its ancillary articles, defined as: an error in the stages of the medication process − ordering, dispensing, administering, and monitoring the effect − causing harm or implying a risk of harming the patient (31).

1.3.2. RISK FACTORS FOR MEDICATION ERRORS

Studies have identified several risk factors for MEs (8,58–62). Risk factors can, regardless of setting, be divided into three groups: 1) Patient-related factors 2) Health provider-related factors and 3) System-related factors (16).

Patient-related factors: In the psychiatric setting, patients often struggle with adherence to their medications. Though this is not always a medication error, it is strongly correlated to worsening of symptoms and rehospitalisation (63).The prevalence of substance abuse is higher in psychiatric patients than in the general population, and little is recognised about the clinical consequences of interactions between substance abuse and prescribed medications (64,65). Several psychiatric conditions often reduce the patients' cognitive skills resulting in insufficient

communication about drug effects and side effects (16). Prescribing medication is complicated in psychiatry; the patients may lack trust in hospital staff (66,67), their conditions may be unstable and rapidly change (16), and the number of comorbidities is often high (60). These are all factors which obfuscate understanding medication errors in psychiatry.

Provider-related factors: Decision-making errors are clinical errors, and two of the most frequent factors leading to these errors are insufficient knowledge of the patients clinical status and insufficient knowledge of the medications prescribed (47,61,68). Researchers have suggested that particularly junior physicians are associated with decision-making errors (47,68).

The use of psychotropic pro re nata (PRN) medications is frequent in psychiatric wards and is a contributory factor to exposing patients to high doses of antipsychotics (69,70). A study showed that PRN administrations took place in the acute phase of 82% of all admissions. Additionally, medication-related morbidity was registered for more than a third of all patients receiving PRN drugs (70). The indications and reasons given for prescribing and administering, respectively, does not necessarily complement each other as physicians and nurses have different knowledge and beliefs about PRN medication; for example, 93% of nurses versus 45% of physicians believe hallucinations/delusions is an appropriate indication for PRN treatment with an antipsychotic (71).

Off-label prescribing refers to situations where a medicinal product is intentionally used for a medical purpose, but not in accordance with the authorised product information (72). There is evidence that off-label prescribing in psychiatry is common (73,74). Off-label prescribing is often not supported by evidence (74) and should, therefore, initiate a higher level of attention towards medication safety.

Dispensing medications is also an opportunity for error. However, this has not been studied extensively although a Danish study, relying partially on direct observation rather than chart review, reported that the rate of dispensing error was 1.85/100 opportunities for error (75).

Nurses are responsible for dispensing and administering medications, although several hospitals in Denmark also allow nurses' assistants to dispense and administer medications. Nurses' assistants have been included in the Medicines Act since 2014 and have an independent responsibility when handling medications (76). Nurses have stated some of the following reasons for administration errors: busy work environment, unclear instructions, communication failure, confusion over sound-a-like medications, problematic drug administration area or storage, as well as personal factors (77).

Adequate monitoring of patients is also essential in patient- and medication safety. Both physicians and nurses may fail to provide proper monitoring. For example; in a meta-analysis, the baseline screening for metabolic syndrome was found to be low. Only the measuring of blood pressure was above 50%. In fact, less than 25% of patients had their lipids, and glycosylated haemoglobin (HbA1c) measured (78). In another study, nurses produced insufficient documentation on the effect of PRN medication, making it extremely difficult to evaluate any outcome (79).

System-related factors: Medication discrepancies are frequent various stages in hospital admissions and transitions of care and may lead to adverse events (80,81). A system-related risk factor also involves a lack of pharmaceutical and pharmacological advice in mental health settings (16). However, although studies are focusing on clinical pharmacists interventions so far have shown a reduction in medication errors (81,82) but on the other hand; similar pharmacist-led interventions have not produced solid evidence for improved patient outcomes (83,84).

1.4. POTENTIALLY INAPPROPRIATE PRESCRIBING IN PSYCHIATRY

PIP is a term mainly used in the research literature on geriatric populations but is relevant for any patient population. Several researchers have examined PIPs in the elderly and have used similar but still slightly different definitions (85–88). The term 'potentially' signifies an understanding of prescribing as a somewhat subjective process influenced by evidence, personal experience, and attitudes as well as patients' preferences (37,89). 'Inappropriate' (or appropriate) refers to the quality of prescribing and provides for more perspectives on prescribing than merely reducing it to a question of good/bad prescribing (90). PIP is a commonly used notion in medication safety, yet difficult to define precisely. However, in this thesis, PIP is defined as:

'…prescribing that introduces a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for the same condition. Additionally, PIP includes the use of drug combinations with known drug–drug interactions, drug–disease interactions, overdosing, use of drugs for a longer time than clinically indicated, as well as the omission of prescribing drugs that are clinically indicated.' (36,37)

1.4.1. IDENTIFYING A POTENTIALLY INAPPROPRIATE PRESCRIPTION

Medication review is often used to detect PIP (91). Currently, there is no 'golden standard' on how, or by whom, medication reviews should be conducted (92,93). However, a recent review a definition: a systematic assessment of the pharmacotherapy of an individual patient that aims to evaluate and optimise patient medication (or not) in prescription, either by a recommendation or by a direct change (92). This is only partly consistent with the understanding of medication reviews in this thesis as recommendations and changes were not part of the study design. Identifying PIPs has much in common with identifying medication errors. However, the research has tended to focus on the use of screening tools to identify PIPs and only in elderly populations. A recent review of published tools to identify PIPs in the elderly found a total of 46 tools which were divided into explicit, implicit and mixed approaches (94). Examples of screening tools frequently used in research are the Beers criteria (95), STOPP and START (96). There are no similar tools or criteria published for the identification of PIPs in psychiatric populations.

Explicit approaches are often designed as 'checklists' to detect PIPs (97–101). Some of the advantages of explicit medication reviews are that they are cheap, simple, easy to apply and objective (89,90); disadvantages include not considering patients' clinical situation and not addressing all aspects of prescribing, e.g. duration of therapy (89).

Implicit approaches include assessment tools such as the MAI-criteria which consist of ten questions used to assess the medication appropriateness of the medication (102) as well as the general medication review. Implicit medication reviews include all the medications prescribed to the patient, the patient's history, the patient's preferences, the best available evidence, and the experience and knowledge of the individual clinician (90,103). However, the method is more susceptible to subjectivity in assessment and, thereby, interrater variation (89,90,104)

Mixed approaches combine the advantages related to implicit and explicit approaches, and also the disadvantages.

In this thesis and its ancillary articles, PIPs are, classified into categories adapted from the error types in the decision-making stage of prescribing given in Appendix A. The resulting categories are shown in Appendix B.

1.4.2. RISK FACTORS FOR PIPS

There is a major overlap between the risk factors for MEs and PIPs. Descriptions of the patient-, provider-, and system related risk factors for MEs are found in Section 1.3.2. Risk factors for PIPs in psychiatry in general have not been investigated,

although, at least three recent studies have examined PIPs in elderly psychiatric patients, looking into the prevalence and risk factors of PIPs (105–107). The prevalence of PIPs, depending on the screening tool, was 53%-79% (106,107). All studies identified psychotropic drugs and polypharmacy as being associated with PIPs. Other risk factors identified were cognitive impairment, previous falls and hospitalisations, somatic comorbidity and living in an institutional setting (105).

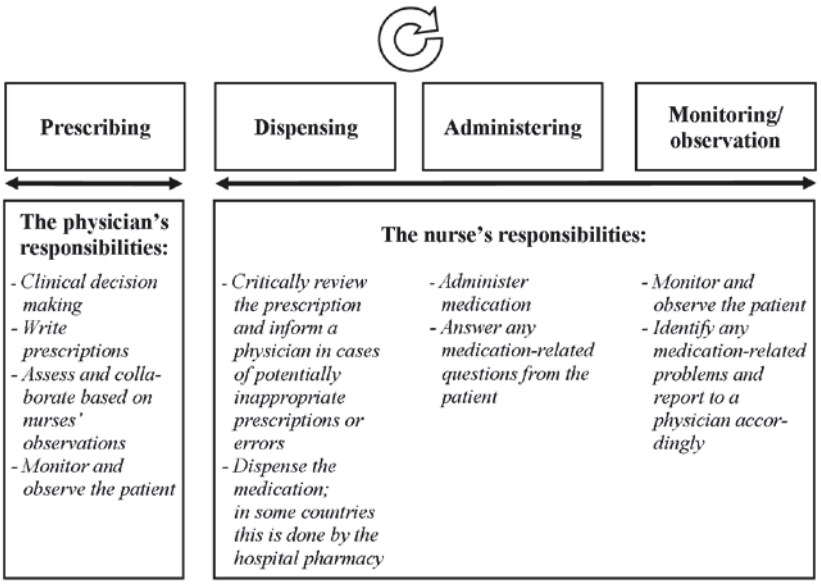
1.5. NURSES AS CONTRIBUTORS TO SAFER PRESCRIPTIONS

Studies have demonstrated associations between levels of nurse staffing and a number of patient outcomes (108–111). Nurses are often the final barriers between the patient and dangerous situations such as medical errors (112). The nurse's role as a safeguard has been examined in several studies; primarily in the intensive care setting (112–115). A report from the UK pointed out the positive correlation between the in patient to staff ratio and mortality in 14 NHS trusts that had performed below the general standard on mortality indicators (116). Exactly how nurses reduce mortality is not clear (117).

Nurses create medication errors as well as intercept them (23,75,77,113,118–120). As described earlier, the medication process consists of prescribing, dispensing, administration, and monitoring. The physician's and nurses' responsibilities in the medication process are illustrated in Figure 1-1.

Occasionally, the medication process will be circular as the physician may alter the patient's medication based on the nurse's observations. Research into the identification of PIPs has so far been limited to elderly populations and almost exclusively carried out by pharmacists. However, nurses are expected to review prescriptions for correctness (is it what the physician prescribed?) before administering the medication. However, at this stage nurses are in a position to critically review the appropriateness of the prescription using the available information technology as well as the clinical knowledge and experience of the individual nurse.

Figure 1-1. The responsibilities of nurses and physicians across the medication process. Source: own contribution.



1.6. NURSE-PHYSICIAN COLLABORATION IN PSYCHIATRIC IN-PATIENT CARE

The NPC in psychiatry is largely unexplored. Studies, in settings other than psychiatry, demonstrate how a poor NPC adversely affects patient outcomes adversely by jeopardising the quality of care and patient safety, leading to increased mortality (121,122). It has been suggested that effective NPC might have a significant positive impact on patient outcome (123).

Ineffective NPC has consequences for both nurses and physicians. Research shows how poor NPCs affects nurses, leading them to become increasingly dissatisfied with their jobs, wanting to leave and find occupation elsewhere (121,124). Physicians described their frustration when orders were not carried out in a satisfactory manner or the communication between the two parties was unclear; they described this frustration as a major source of job dissatisfaction (121).

An analysis of nurses and physicians collaboration in the stages of prescribing and administering medications revealed that when physicians and nurses do rounds together, the physician benefits from the nurse's knowledge about the patient and the nurse possesses a better understanding of the patient's medical case and the decision-making process behind each prescription (125). According to Reason, the well-known author of literature on human error, safety is about relationships – which is about teamwork (54). Working in teams requires a levelling of hierarchy and mutual respect, based on good communication (13).

Disruptive behaviour from physicians or nurses is a poorly defined phenomenon but isgenerally understood as a hostile, intimidating behaviour characterised by poor communication. Though most research on the subject has focused on physicians, nurses may also display disruptive behaviour (126). Physicians, when displaying disruptive behaviour, tend to be direct and overt; for example shouting, acting offended and rolling their eyes. Nurses' disruptive behaviour is often of a more passive-aggressive nature; for example being 'backstabbing', fault-finding and 'back-door undermining' (126,127). NPC, whether disruptive or supportive and respectful, is thus an important factor in medication safety (124,126,127).

In this thesis, NPC is defined as:

'Actions related to sharing information about patients, participating in decision-making concerning patient care, and providing comprehensive care to patients from a patient-centred perspective.' (128)

1.7. LITERATURE SEARCH

The databases Pubmed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) with full text and PsycINFO were searched to identify literature relevant to the four studies. Languages were restricted to English and Scandinavian. The databases were searched up to and including 2016. Where available, Medical Subject Headings (MeSH), and CINAHL Headings and Subject Headings were used. Alternatively, search terms were entered as free text. Limits were applied using "human participants" and no time restrictions were applied. The following search terms were combined in structured searches:

'safety', 'patient safety', 'medication safety', 'medication errors', 'adverse drug events', 'psychiatry', 'psychiatric', 'mental', 'mental health', 'nurses', 'psychiatric nursing', 'potentially inappropriate prescribing', 'inappropriate prescribing',

'physician-nurse relationship', 'physician-nurse collaboration', 'intercollaboration', 'interprofessional', 'behaviour', 'behavior', 'disruptive behavior', 'outcome', 'patient outcome'.

The search also included other sources: webpages of official authorities, health authorities, health organisations, and reference lists from relevant literature.

1.8. EXISTING LITERATURE AND LIMITATIONS

1.8.1. STUDY I (ERRORS IN THE MEDICATION PROCESS)

The latest review on medication errors in mental health settings concluded that the evidence was limited and also commented on the problems inherent in comparing the incidence and prevalence of medication error outcomes when methodologies vary (16). The most reliable and valid methodologies used, to study medication errors, have been scrutinised in several papers (41,45,48–52). Studies investigating errors, in all stages of the medication process in psychiatry are few and do not consistently rely on the most sensitive methods (17,129–131).

Some studies have focused on prescribing errors (132–138), and others on administration errors (77,136). The literature demonstrates that errors in the medication process are frequent, however, establishing the prevalence and incidence and types of error are highly difficult (16,139). Moreover, medication errors in psychiatry do cause harm but tend to be less serious or fatal than in general hospital settings (17).

All studies retrieved from the literature search were from the US, UK, or Japan, and their applicability to Danish settings are unknown.

To date, in psychiatry, there have been no studies of errors in all stages of the medication process using the most valid and sensitive methods. Moreover, in Denmark, no studies in psychiatry have focused on medication errors.

Therefore, a cross-sectional study was designed to detect errors in all stages of the medication process. In line with the literature, the most appropriate methods for identifying errors were chosen in each stage of the medication process.

1.8.2. STUDY II (CHARACTERISTICS OF PIPS)

Many studies point to PIP as a significant problem in the elderly causing unnecessary hospital admissions, increased morbidity and even mortality (140). The elderly are often at risk of PIP due to increased morbidity, complex medication regimens with many concurrent prescriptions and age-related changes in physiology, such as diminished renal capacity and changes in liver metabolism (36,90). Psychiatric patients do not necessarily share the elderly's vulnerabilities. However, psychiatric patients have a life expectancy 15 – 20 years shorter than the general population – often due to somatic illness (141,142). Psychiatric patients also suffer challenges such as unpleasant side effects to their medication; examples being diabetes, obesity, hypercholesterolemia, and related morbidity such as heart disease (143–145). All of which emphasise the importance of appropriate medications for psychiatric patients. However, reports indicate that inappropriate prescribing defined by explicit categories such as antipsychotic polypharmacy, high-dose antipsychotics, and high-dose benzodiazepines are frequent and problematic (18,19,146).

To the best of our knowledge, the majority of studies reviewed so far, suffer the limitation of not considering the general psychiatric patient. When studies include general psychiatric patients, they do not consider the entire medication regimen for each patient but rather a defined category of inappropriate prescribing.

Therefore, a cross-sectional study aiming to identify and describe PIP was undertaken.

1.8.3. STUDY III (NURSES AND PIP IDENTIFICATION)

Many nurse-led interventions have demonstrated a positive effect on a range of patient outcomes such as improving survival in patients with heart failure, reducing hypertension, controlling anticoagulant treatment, and the management of patients with lung cancer (147–151). Studies indicate that nurses beside improving psychiatric patients adherence also improve the assessment of individual needs and treatments (152–154). Previous research findings also report nurses positively participate in and improve pharmacovigilance; at least in Sweden (155–157).

Although nurses are involved in the multidisciplinary collaboration surrounding the medication process, only a few studies have investigated nurses capacity for systematically detecting and preventing medication-related problems (23,24,158). These studies indicated that nurses were able to identify and respond to relevant problems related to elderly patients' medication. One small Japanese study has investigated nurses' collaboration with physicians in managing medication in psychiatric care (154). This controlled interventional study demonstrated an improvement in schizophrenic patients' social functioning as well as a number of

other measures, when physicians changed medication after receiving reports that nurses perceived a change was necessary. However, the study suffered some limitations due to a retrospective design. Another study showed a positive impact of a medicines management course to nurses on patient outcomes (158). The study was designed as a randomised controlled trial, but assessed only the efforts of the nurses on patients' adherence to medication and the consequently clinical outcome for the patients on the Positive and Negative Syndrome Scale (PANSS).

Therefore, an interventional, controlled study was undertaken, placing nurses centrally in identifying and reporting PIP after a pharmacology course, was conducted in order to investigate nurses' skills and potential improvements in prescribing quality.

1.8.4. STUDY IV (NURSE-PHYSICIAN COLLABORATION)

Before implementation of any patient safety practice, it is necessary to consider the context in order to evaluate the possibility of similar outcomes in different settings (159). If nurses' observations and knowledge of patients' unique situations are to lead to improvements in prescribing, NPC has to in place, as physicians have the primary responsibility for patients' prescriptions. This raises questions about NPC in psychiatry, and particularly in relation to medication optimisation.

Evidence from general hospital settings suggests a positive correlation between the NPC and patient outcomes (122,124,126,160). I identified a few studies of NPC in psychiatric settings; this literature emphasised that a positive NPC is associated with improved patient outcomes and fewer adverse events to patients and staff (154,161,162). Additionally, strong nurse-physician relationships as significantly associated with lower rates of psychiatric nurse burnout (163). However, there are few studies directly addressing the influence of NPC in medication optimisation in psychiatry.

As a result, a qualitative study using focus groups was carried out to explore the perceptions and views of nurses collaborating with physicians on medication optimisation in a psychiatric hospital.

CHAPTER 2. HYPOTHESES AND OBJECTIVES

The overall aim of this thesis was to investigate medication safety for psychiatric patients and nurses' possible role in improving medication safety. Failing medication safety must be understood comprehensively and including errors in the medication process, medication errors, PIPs, and the views and perceptions of individuals. The four studies comprising this thesis all investigate an aspect of medication safety and together provide evidence for understanding the dimensions of medication safety, prescribing patterns, and nurses' preventive and mitigating role in prescribing for psychiatric patients.

I developed the following hypotheses and the adjacent objectives based on the previously described literature search.

2.1. STUDY I (ERRORS IN THE MEDICATION PROCESS)

Hypothesis: Errors in the medication process in psychiatric hospitals are frequent and similar to the prevalence found in general hospital settings.

Objective: To evaluate the prevalence, types, and potential clinical consequences of errors in the medication process in psychiatric wards.

2.2. STUDY II (CHARACTERISTICS OF PIPS)

Hypothesis: Psychiatric inpatients experience PIPs at the point of admission, the presence of PIPs are associated with age, gender, alcohol- and substance abuse, polypharmacy (more than five prescriptions) and somatic illness.

Objective: To evaluate the prevalence, types, and predictors of PIP as well as the severity of potential clinical consequences.

2.3. STUDY III (NURSES AND PIP IDENTIFICATION)

Hypothesis: Nurses can identify PIPs in psychiatric patients' medication lists and their reports to physicians lead to relevant changes to prescriptions.

Objective: To examine the characteristics, magnitude, and potential effect of pharmacologically trained nurses' systematic review of medication records on the appropriateness of prescribing for newly admitted psychiatric patients.

2.4. STUDY IV (NURSE-PHYSICIAN COLLABORATION)

Hypothesis: Collaboration between nurses and physicians can be improved.

Objective: To explore how nurses perceive collaborating with physicians on medication optimisation for psychiatric patients.

CHAPTER 3. METHODS

The studies in this thesis all took place in the Psychiatric Department of Aalborg University Hospital, Denmark. The Psychiatric Department serves the entire North Denmark Region and is organised in two clinics: Clinic South and Clinic North. The North Denmark Region contains approximately 580,000 citizens, and every year the clinics receive close to 2,800 adults. The individual units specialise in acute psychiatry, bipolar disease and depression, psychotic illnesses, and personality- and anxiety disorders (164). This thesis is based on data from chart reviews (Study I), direct observation (Study I), medication reviews (Studies II & III), and focus group interviews (Study IV).

3.1. STUDY I (ERRORS IN THE MEDICATION PROCESS)

3.1.1. DESIGN

Study I was a descriptive, cross-sectional study of errors and potential harm in the medication process. This study included both regular and PRN prescriptions except in discharge summaries. Three different methods for collecting data were applied: direct observation, unannounced visits to the wards to collect dispensed drugs for identification, and chart review to detect the most reliable and valid estimates of errors in each stage of the medication process (48,49,51).

3.1.2. SETTING

Study I was carried out from January 2010 to April 2010 in three bed units in the Psychiatric Department, Clinic South, Aalborg University Hospital, Denmark.

3.1.3. STUDY POPULATION

The observational unit involved any handling of medication (prescribing, dispensing, and administering medication). The study population investigated comprised patients ≥18 years old admitted to the participating bed units, physicians prescribing medication, nurses and nurses' assistants dispensing and administering medication. There were no exclusion criteria applied.

3.1.4. DATA COLLECTION

Observation

Direct observation was used to identify errors in the dispensing and administration stages. One of the investigators (ALS) observed nurses and nurses' assistants who dispensed and administered medications. The same investigator spent three eight-hour shifts (two-day shifts and one evening shift) in each ward. The nurse or nurse assistant being observed had knowledge of the study's purpose but was not informed about what observations were being registered. Observations of the dispensing or administering of drugs were registered on a structured paper form and compared to the prescriptions in the EMR to identify discrepancies. The investigator classified any discrepancy as an error which was categorised according to the error types outlined in Appendix A.

Unannounced visit

The unannounced visit served as an unbiased method to identify errors in the dispensing stage. The use of two methods in the dispensing stage, observation and unannounced control visits, was intended to validate the results from the observational part of the study. The unannounced visit was used to identify errors in the dispensing stage without the nursing staff being aware of an imminent check of their actions. One of the investigators (ALS) arrived unannounced to the bed units, approximately three weeks after the observational part of the study, and collected medication from the medication storage room after the dispensing had taken place, but before administration. The investigator followed up by identifying and comparing the dispensed medications (using an authorised webpage (http://pro.medicin.dk/)) to the patient's prescriptions in the EMR. The investigator classified any discrepancy as an error and categorised it according to the error types outlined in Appendix A.

Chart review

Chart review was used to identify errors in the prescribing stage, including discharge summaries. One of the investigators (ALS) compared prescriptions in the EMR to the error types outlined in Appendix A. The investigator screened all prescriptions the first time a patient's chart was reviewed; if the same patient's chart was reviewed more than once only new or altered prescriptions were screened for errors. Only errors in the communication of a prescription were included.

Assessing potential severity of errors

The SCPPs assessed the severity of each error identified in the communicating of an error in the prescribing stage, as well as those in the dispensing and administering stages. Because of logistic issues, errors in discharge summaries were not assessed for potential severity. The SCPPs utilised a four-point scale (non-significant, significant, serious, and fatal) first published by Lisby et al. (165) to

assess the potential severity of the errors and PIPs (see Appendix D for elaboration of the categories of potential clinical consequences).

3.1.5. STATISTICAL ANALYSIS

A defined denominator was required to enable the calculation of proportions of errors (31). 'Opportunities for error' (omissions, mistakes, and/or conscious or unconscious rule violations) was chosen as this denominator. All data analysis was performed using Stata/IC versions 13.0 (Statacorp, College Station, TX, USA). Frequency tables were used to show prevalence, proportions of errors, and error types in the different stages of the medication process. Interrater reliability for the SCPPs' evaluations of severity of potential clinical consequences was calculated when appropriate, using the kappa test.

3.2. STUDY II (CHARACTERISTICS OF PIPS)

3.2.1. SETTING

Study II was carried out from 1 September to 31 November 2013 in the Psychiatric Department, Clinic South, and Clinic North, Aalborg University Hospital, Denmark.

3.2.2. DESIGN

Study II was a cross-sectional, descriptive study of PIPs, potential harm, and possible predictors of PIPs. The method of data collection comprised medication reviews by SCPPs.

3.2.3. STUDYPOPULATION

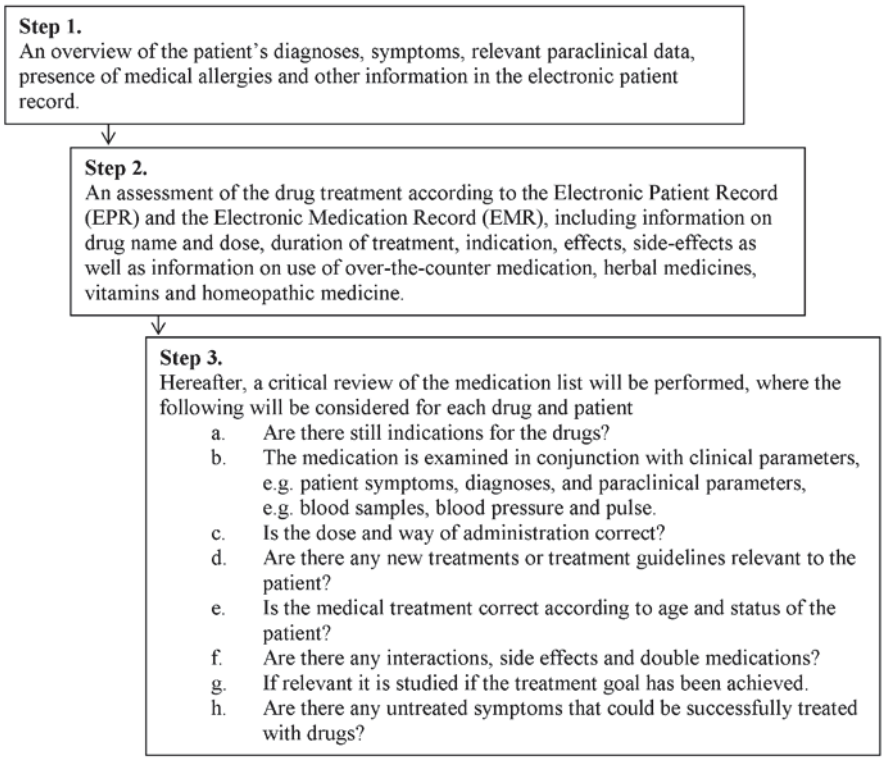
Study II (Characteristics of PIPs), included all patients ≥18 years admitted because of any psychiatric condition. Exclusion criteria were terminally ill patients with an anticipated short life expectancy, dual admissions to hospitals other than psychiatric, non-obtainable medical records, and no prescriptions. Forensic patients and child/adolescent patients were not included.

3.2.4. DATA COLLECTION

Medication review

Two SCPPs (LPN and BKP) carried out all medication reviews following a procedure adapted from a Danish Ph.D. thesis (166) in which medication reviews by clinical pharmacologists also played a role. The procedure is illustrated in Figure 3-1.

Figure 3-1. The process of medication reviews by clinical pharmacologists. Adapted from 'Potentially inappropriate prescriptions in patients admitted to psychiatric hospital', Nordic Journal of Psychiatry, copyright © Nordic Psychiatry Association. Reprinted with permission from Taylor & Francis Ltd, www.tandfonline.com on behalf of the Nordic Psychiatry Association.



The original procedure devised by Bonnerup et al. (166) included patient involvement and recommendations for ward physicians, but these were excluded in the present study. The SCPPs categorised all identified PIPs. The 14 categories can be seen in Appendix B. Additionally, the SCPPs carried out an assessment of

severity of each PIP identified in the decision-making stage of prescribing. For the assessment of severity of the PIPs, the SCPPs utilised the same method described under Study I, Section 3.1.4.

3.2.5. STATISTICS

In Study II, frequency tables were used to show the prevalence, categories, and potential clinical consequences of PIPs as well as the characteristics of the patients in the study populations. A logistic regression model was used to identify potential predictors of PIPs. The model predicted the odds of having versus not having one or more PIP and was adjusted for age, gender, alcohol or substance abuse, the number of prescriptions and somatic illness. The results are presented as odds ratios (OR) with 95% confidence intervals (95% CI). Statistical significance was set at an alpha level of 0.05. All analysis of data was performed using Stata/IC version 14.0 (Statacorp, College Station, TX, USA).

3.3. STUDY III (NURSES AND PIP IDENTIFICATION)

3.3.1. SETTING

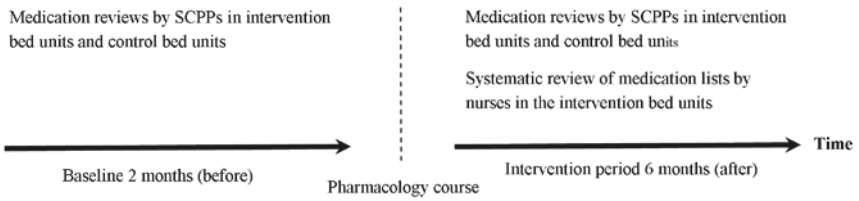
Study III was carried out from 1 November 2014 to 30 June 2015 in the Psychiatric Department, Aalborg University Hospital, Denmark. Two bed units served as intervention units and two bed units as control units, from Clinic South and Clinic North, respectively.

3.3.2. DESIGN

Study III was a controlled, interventional before-and-after study investigating the potential effect of pharmacologically trained nurses' systematic reviews of medication records, on the reduction of PIPs for psychiatric patients at the point of admission. Patients in the control bed units received 'care as usual' throughout the study. 'Care as usual' included physicians carrying out a medication review in addition to examining the patient. Patients in the intervention bed units also received 'care as usual', but in addition to this, nurses who had attended a pharmacology course reviewed the patients' medication records. If the nurses identified what they perceived to be a PIP, they would present their observation to a physician who would then decide on any further action. SCPPs carried out medication reviews on all patients included in the study from start to finish. The SCPP-led medication reviews provided a baseline period (the before) to compare any changes or differences during the intervention period (the after) both within and

across the control and intervention bed units. Additionally, the SCPP-led medication reviews provided a 'gold standard' against which the nurses' identifications of PIPs was validated. A description of the methods of medication reviews, the nurses' pharmacology course, and the recording of the nurses' observations is found in Section 3.3.4. Figure 3-2 illustrates the study design. Bed units were selected based on matched age categories and diagnoses to ensure comparability across control and intervention bed units.

Figure 3-2. Illustration of the study design.
Source: own contribution.



3.3.3. STUDY POPULATION

Study III included all adult patients admitted due to any psychiatric condition. Exclusion criteria were terminally ill patients with an anticipated short life expectancy, an expected length of stay of less than 48 hours, patients transferred from another psychiatric unit or who had previously been included in the study, and eligible patients where the nurses failed to review the medication list.

3.3.4. DATA COLLECTION

Medication reviews

Two SCPPs (LPN and BKP) carried out all medication reviews which followed the same procedure as in Study II (see Section 3.2.4 and Figure 3-1). The original procedure presented by Bonnerup et al. included patient involvement and recommendations for ward physicians, but this was excluded in Study III in this present thesis. The SCPPs categorised all identified PIPs according to type (see Appendix B). In Study II, the SCPPs utilised 14 types of PIPs which were changed to 15 types of PIPs in Study III. In Study II 'omission of Therapeutic Drug Monitoring (TDM))' was classified as 'other'; but it became evident that valuable information could be gained by isolating 'TDM' from 'other' resulting in 15 types of PIPs in Study III. In Study III, the SCPPs carried out medication reviews during baseline (the 'before') and the intervention period (see Appendix C for the paper

form used by the SCPPs to record their medication reviews). For the assessment of severity of the PIPs, the SCPPs utilised the same method as described under Study I, Section 3.1.4

3.3.5. THE INTERVENTION – A PHARMACOLOGY COURSE AND NURSES' SYSTEMATIC OBSERVATIONS

The pharmacology course

Before the testing of the intervention, all nurses from the intervention bed units received a five-day course on general pharmacology and psychopharmacology. The course also included treatment principles for some of the major mental disorders, principles of medication review, exercises in identifying PIPs, and how to register systematic observations. The course programme can be seen in Appendix E. Classes given at the course were delivered by the SCPPs (BKP and LPN), who also performed all the medication reviews alongside the nurses in the intervention, but lecturers also included psychiatrists, physicians, a pharmacist and the course leader (ALS).

Nurses collecting observations of PIPs

After the pharmacological course, the intervention was initiated. Patients were included consecutively in the order they were admitted to the bed unit. As soon as possible, after the patient had been examined by a physician, the nurses would critically review the patients' medication list, using their experience, skills learned during the pharmacology course, and any additional knowledge they might have acquired about the patient's situation. All observations of what the nurses considered a PIP were recorded on a paper form (see Appendix F).

3.3.6. STATISTICS

In Study III, frequency tables were used to show the prevalence, categories, and potential clinical consequences of PIPs, as well as the characteristics of the patients in the study population. To detect an absolute reduction of 20 percentage points in patients receiving at least one PIP, at a two-sided 0.05 significance level, a sample size of 100 patients per group during the intervention period was needed to ensure 80% power. The power calculation was based on findings in Study II (167) and a reduction of 20 percentage points was considered clinically relevant. Interrater reliability between the SCPPs' and nurses' assessments of whether or not a patient had at least one PIP was calculated using the kappa test. Difference in means was compared using the Wilcoxon rank sum test due to non-parametric data. Both linear and logistic regression analyses were applied to estimate a difference-in-difference (DID) between intervention and control bed units for the mean number of PIPs per patient and the number of patients receiving $\geq$1 PIP. Difference-in-difference represents the coefficient for the interaction between intervention and control bed

units, and time (before/after). Data analysis of data was performed using Stata/IC version 14.0 (Statacorp, College Station, TX, USA).

3.4. STUDY IV (NURSE-PHYSICIAN COLLABORATION)

3.4.1. SETTING

Study IV was carried out at The University College of North Jutland, Denmark. The first focus group was assembled 21 December 2014 and the second focus group was assembled 5 January 2015.

3.4.2. DESIGN

Study IV comprises a qualitative focus group study. Two focus group interviews with nurses were carried out. The focus groups mixed participants from both participating bed units. Focus group interviews was the approach because the aim was to uncover aspects of collaboration between healthcare professionals and thus involved groups (168). More specifically, the aim was to explore the nurses' perceptions of collaborating with physicians on medication optimisation in psychiatric bed units; this involves rules and values within and between professions and groups. These complex systems of collaboration might depend on local characteristics and cultures which was the reason for including nurses already familiar with each other, even though focus groups usually consist of individuals, who do not know each other (169). However, the design of the study also allowed for nurses not familiar with each other to engage. This choice of 'mixing the bed units' was developed to investigate social processes and possibly group interactions that would stimulate certain ideas or perhaps communication suppressed by the group (170).

Preparation for Study IV included a pilot test of the structured interview guide. Participants were nurses from an acute psychiatric bed unit who frequently collaborated with nurses from the two bed units participating in the present study. The pilot test did not prompt any significant changes to the interview guide.

3.4.3. STUDYPOPULATION

The study population included all nurses who had previously participated in a mandatory five-day long training programme on general pharmacology, psychopharmacology, and medication safety. The nurses came from bed units specialising in psychotic disorders and affective disorders.

3.4.4. DATA COLLECTION

In Study IV, the approaches used to collect data were a semi-structured interview guide, audio and video recordings, and field notes. The semi-structured interview was guided by the following themes:

- Experiences and thoughts of collaborating with physicians about patients' medications.
- Self-perceived influence on NPC about medication optimisation and factors modifying this.
- Nurses' thoughts and perceptions of their needs for pharmacological knowledge and their possibilities for advocating safer medication of patients within the NPC.

The interviews were planned to last 60-90 minutes. The interviews took place immediately after the nurses completed the pharmacology course described under Study III (see Section 3.3.5). Before the interviews, the participants, and the interviewer had established a relationship during the pharmacology course, and the participants were aware of the interviewers' areas of interest such as medication safety, nursing, and mental health. However, the interviewer took extensive measures not to share or disseminate any personal or professional opinions during the pharmacology course. All efforts were aimed at establishing an environment that encouraged speaking and interaction between the nurses without restrictions. Only participants and the interviewer were present during the focus groups. Each focus group began with a relatively broad approach, making it possible to discuss a variety of nursing-related issues. The interviewer then moved on to the semi-structured interview guide which was designed to unveil the respondents' experiences, thoughts, and perceptions, both positive and negative.

The interviews in Study IV were recorded with a digital camcorder and a digital audio recorder to ensure two modalities of data in cases of uncertainty. The interviewer (ALS) transcribed all recordings. All transcribing was checked by an independent researcher not related to the project in any way, to check for consistency with both audio and video recordings.

The interviewer wrote field notes immediately after each focus group that documented her observations of moods, tendencies, and insights.

3.4.5. THEMATIC ANALYSIS

Data analysis in Study IV was carried out in NVivo 11. The qualitative analysis applied to data involved inductive thematic analysis (171). The analyses were performed in four steps. Firstly, ALS repeatedly read the transcripts, searching for

meaning and inspiration for incipient coding. Secondly, these initial codes and selected field notes were presented to and discussed with other researchers involved in the study until an agreement was reached on relevant codes. Thirdly, ALS continued to form themes from the coded data, and finally, the themes were reviewed until an agreement on the accuracy of themes was reached. The analysis followed the Consolidated Criteria for Reporting Qualitative studies whenever possible (see the checklist in Appendix G).

3.5. STUDY DESIGNS

Figure 3-3 gives an overview of study designs and methodologies used in this thesis.

Figure 3-3. Overview of study design and methodology of the studies on which the thesis is based.
Source: own contribution.

	Study I	Study II	Study III	Study IV
Design	Cross-sectional	Cross-sectional	Interventional before-and-after	Qualitative focus group interview
Data collection method(s)	Observational Unannounced visit Chart review	Medication review Chart review	Medication review Nurses observations	Audio recording Video recording Field notes
Data	Demographics Diagnosis codes PIPs	Demographics Diagnose codes PIPs	Demographics Diagnose codes PIPs Nurse-reported PIPs	Transcriptions
Participants	Patients admitted to a bed unit, physicians, nurses, nurses assistants	Patients admitted to a bed unit	Patients admitted to a bed unit	Nurses
Outcome	Prevalence, type, and severity of errors in the medication process	Prevalence, types, and severity of PIPs Potential risk factors	Potential improvement in PIPs based on nurses observations	Nurses' views and perceptions of nurse-physician collaboration in medication optimisation
Analysis	Descriptive statistics Kappa test	Descriptive statistics Logistic regression	Descriptive statistics DID using regression analysis	Qualitative thematic analysis

DID: Difference-in-difference; PIP: Potentially inappropriate prescriptions

CHAPTER 4. ETHICS

The studies in this thesis did not require permission from The Danish Scientific Ethics Committee as patient contact was not involved.

The following approvals were acquired before initiating the studies:
Study I: was approved by The Danish Data Protection Agency (record number: 2009-41-4215) and the hospital management. Participating staff were informed of the study's purpose.

Study II: was approved by the Danish Health and Medicines Authority (record number: 3-3013-118/1/), The Danish Data Protection Agency (record number: 2012-41-0369), and the hospital management.

Study III: was approved by the Danish Health and Medicines Authority (record number: 3-3013-118/1/), The Danish Data Protection Agency (record number: 2012-41-0369), and was registered with clinical.trials.gov (record number: NCT02052505). Participating staff were informed of the study's purpose.

Study IV: was approved by the hospital management and participation was voluntary. All participants gave oral consent to the study.

CHAPTER 5. RESULTS

The following sections describe the main results from the four studies upon which this thesis is constructed. Appendices at the back of the thesis contain additional material relevant to the results.

5.1. STUDY I (ERRORS IN THE MEDICATION PROCESS)

The analysis in Study I included 67 patients; 24 (36%) men and 43 (64%) women. The mean age was 46 (IQR; 20-79) and the most common psychiatric disorder at admission was schizophrenia 22/67 (33%). Second most frequent psychiatric disorder at admission was bipolar disorder 11/67 (16%).

5.1.1. FREQUENCY OF ERRORS AND ERROR TYPES

Overall, 189 errors in 1082 opportunities for error were identified, generating an error rate of 17%. Table 5-1 presents frequencies of errors in the different stages of the medication process.

Table 5-1. Frequency of errors in the different stages of the medication process. (Reprinted from Risk Management and Healthcare Policy, Volume 6, Soerensen AL, Lisby M, Nielsen LP, et al.,'The medication process in a psychiatric hospital: are errors a potential threat to patient safety?', p.23-31, copyright (2013), with permission from Dove Medical Press Ltd.)

Prescribing, CPOE n/N_{total}(%)	Dispensing, observational study, n/N_{total}(%)	Dispensing, unannounced visit, n/N_{total}(%)	Administration, n/N_{total}(%)	Discharge summaries, n/N_{total}(%)
10/267 (4)	9/324 (3)	9/67 (13)	142/340 (42)	19/84 (23)

Notes: N_{total} = the total number of opportunities of errors in each stage (prescription and doses); n, the total number of detected errors in each stage of the medication process. The difference in number of dispensed medications and administered medications in the observational study was due to incidents where staff had administered medicine without the investigators presence.
Abbreviation: CPOE, Computerized Physician Order Entry.

The highest proportion of errors was found in the administration stage 142/340 (42%) followed by discharge summaries 19/84 (23%). The leading error type in the

administration stage was lack of identity control 135/142 (95%). Nine errors in discharge summaries were eligible prescriptions in the Computerised Physician Order Entry (CPOE), which was not extended to the discharge summaries. In the discharge summaries, where 19 errors were identified, the most frequent error type was *'drug prescription'* 9/19 (47%) and *'omission of drug'* 9/19 (47%). *'Drug prescription'* includes errors in writing of a prescription, e.g. strength per unit, route of administration, form of administration, dose, frequency of administration, signature, date, and duration of treatment.

Two methods, observation and unannounced visit, were used to investigate the dispensing stage, generating a proportion of errors of 9/324 (3%) and 9/67 (13%), respectively. In the dispensing stage, the most frequent error type identified through observation was *'lack of correct labelling'* (4/9), whereas the most frequent error type identified through unannounced visit was *'omission of dose'* (6/9). *'Lack of correct labelling'* means that all drugs administered to patients must be marked with the patient's identity. Most errors in the unannounced control visit were associated with one nurses' assistant.

The prescribing stage presented the lowest proportion of errors, 10/267 (4%) and the most frequent error type was '*omission of PRN dosing'* in the CPOE (8/10).

5.1.2. POTENTIAL CLINICAL CONSEQUENCES

Analysis of the assessments of potential clinical consequences applied a worst case scenario; if the clinical pharmacologists disagreed on the severity of an error, the most severe assessment was recorded for the analysis. The clinical pharmacologists did not assess errors in discharge summaries; thus the number of opportunities for error was reduced to 998 in the analysis of potential clinical consequences. Definitions on the rating of potential clinical consequences are outlined in Appendix D.

Interrater agreement for potential clinical consequences of errors in the prescription stage, errors in the dispensing stage in the observational part of the study, errors in the dispensing stage investigated with unannounced visit, and the administration stage, varied from good to perfect (0.54; 0.75; 0.82 and 1.0, respectively). The clinical pharmacologists assessed 84/998 (8%) opportunities for error as potentially serious or potentially fatal. Thus, according to the applied definition, medication errors were identified in 8% of all opportunities for error throughout the medication process.

As mentioned above, most errors were found in the administration stage and approximately half of these errors, 73/142 (51%) were assessed to have potentially serious clinical consequences for patients. There were four potentially fatal errors in total. Two errors concerned '*omission of PRN regime*' in the prescribing stage and

the remaining two errors were of the type *'lack of identity control'* in the administration stage.

5.1.3. DRUG CATEGORIES

The most frequent drug categories related to potentially harmful errors were atypical antipsychotics, anxiolytic-sedative drugs, and mood stabilisers. Errors assessed as potentially fatal were found in the prescribing and administration stages and involved analgesics (opioids) (n=2) and atypical antipsychotics (n=2). Drugs related to somatic illness and with the potential for harming patients accounted for almost one in ten, 7/77 (9%), and predominantly involved anti-inflammatory and anti-rheumatic drugs.

5.2. STUDY II (CHARACTERISTICS OF PIPS)

This study included 207 patients. The mean age was 42 years with range 18-83. Schizophrenia and other psychotic disorders were the most frequent diagnoses at 77/207 (37%), followed by affective disorders 68/207 (33%). Somatic illness affected little more than a third, 71/207 (33%), of all included patients. The leading categories of somatic disease were cardiac disease, diabetes mellitus 2, and COPD.

5.2.1. POTENTIALLY INAPPROPRIATE PRESCRIPTIONS

Overall, 349 PIPs were identified in 1291 prescriptions. The median number of prescriptions was four but, nonetheless, 26/207 (13%) patients in the study population were prescribed ten or more regular drugs daily. The proportion of patients with at least one PIP reached 123/207 (59%). The proportion of patients with at least one PIP assessed to be potentially harmful was 69/207 (33%) which is higher than the proportion of patients with at least one PIP assessed to be potentially fatal 24/207 (12%). Table 5-2 illustrates categories, frequencies, and severities of potential clinical consequences.

Table 5-2. Categories, frequency, and potential clinical consequences of potentially inappropriate prescriptions (PIPs). (Reproduced from 'Potentially inappropriate prescriptions in patients admitted to psychiatric hospital', Nordic Journal of Psychiatry, copyright © Nordic Psychiatry Association, reprinted by permission of Taylor and Francis Ltd, www.tandfonline.com on behalf of Nordic Psychiatry Association.)

	Total number of PIPs		**Potentially non-significant**		**Potentially significant**		**Potentially serious**		**Potentially fatal**	
Category of PIP	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Interaction between drugs	125	36	2	1	42	34	49	39	32	26
Drug dosage too high	56	16	6	10	24	43	22	39	4	7
Omission of indication for treatment	46	13	26	57	11	24	8	17	1	2
Other	38	11	8	21	12	32	17	45	1	3
Interaction between drug and disease	32	9	1	2	12	38	16	50	3	9
Omission of a potentially useful medication	16	5	1	6	7	44	8	50	0	0
Inappropriate dosing interval	11	3	6	55	4	36	1	1	0	0
Drug dosage too small	8	2	0	0	6	75	1	13	1	13
Allergy	6	21	3	50	1	17	0	0	2	33
Duplicate drug	4	1	0	0	2	50	25	1	25	25
Inappropriate dosage time	3	1	1	33	2	67	0	0	0	0
Inappropriate dosage form	3	1	2	67	1	33	0	0	0	0
Inappropriate duration of treatment	1	1	0	0	1	100	0	0	0	0
Inappropriate route of administration	0	0	0	0	0	0	0	0	0	0
Total (N)	**349**		**56**		**125**		**123**		**45**	

Table 5-3 displays the logistic regression analysis of factors possibly predictive of PIPs.

Table 5-3. Characteristics of patients prescribed potentially inappropriate prescriptions (PIPs) versus those not perscribed PIPs (N=207). (Reproduced from 'Potentially inappropriate prescriptions in patients admitted to psychiatric hospital', Nordic Journal of Psychiatry, copyright © Nordic Psychiatry Association, reprinted by permission of Taylor and Francis Ltd, www.tandfonline.com on behalf of Nordic Psychiatry Association.)

			Adjusted logistic regression analysis[a]		
	Patients with PIP N (%)	**Patients with no PIP N (%)**	**OR**	**95%CI**	**p-value**
Age (reference group: 40-59)					
18-29 years	29 (46)	34 (54)	0.66	0.30-1.44	0.296
30-39 years	26 (68)	12 (32)	1.45	0.59-3.61	0.418
40-59 years	24 (33)	49 (76)	1		
≥60 years	24 (73)	9 (27)	0.77	0.29-2.06	0.602
Gender (reference group: male)					
Male	54 (57)	41 (43)	1		
Female	74 (66)	38 (34)	1.44	0.75-2.76	0.273
Alcohol or substance abuse (reference group: no alcohol or substance abuse)					
No substance abuse	88 (63)	52 (37)	1		
Substance abuse	40 (60)	27 (40)	1.16	0.55-2.42	0.702
No. of prescriptions (reference group : 1-5)	43 (43)				
1-5 prescriptions	85 (79)	57 (57)	1		
≥6 prescriptions	66 (51)	22 (21)	3.66	1.88-7.11	<0.0001
No. of somatic diagnoses (reference group: 0)	62 (79)				
0 somatic diagnoses		63 (49)	1		
≥1 somatic diagnose		16 (21)	2.53	1.17-5.48	<0.018
Pseudo R^2				0.15	

The reference group is the category to which all other categories are compared for each variable. CI: confidence interval; OR: odds ratio. The OR reflects the association between the odds for at least one PIP and the interaction of each variable. [a]Adjusted for age, gender, substance abuse, number of prescriptions, and number of somatic diagnoses using logistic regression considering each patient as a cluster (N=207).

Only polypharmacy (>5 prescriptions) and having one or more somatic diagnoses affected the risk of PIPs. No other variable appeared as an important confounder or predictor of PIPs.

When performing subgroup analysis where potentially severe and potentially fatal PIPs were analysed together, patients with polypharmacy (>5 prescriptions) had a more than doubled risk of potentially harmful PIPs (RR=2.42, 95%CI=1.64 – 3.56) compared to patients receiving <5 prescriptions. A comparison of patients with somatic diagnoses and patients without somatic diagnoses yielded an almost twice as high relative risk (RR) of potentially severe or potentially fatal PIPs (RR=1.96, 95%CI=1.41-2.72). Antipsychotics were the unconditionally most prevalent drug category associated with the potentially serious or potentially fatal PIPs.

Antipsychotics and antidepressants were the most frequent drug categories associated with potentially serious and potentially fatal PIPs. However, drugs used to treat somatic conditions were also associated with potentially serious and potentially fatal PIPs. Some examples are non-steroidal anti-inflammatory drugs (NSAIDS), antibiotics, and beta-blockers.

5.3. STUDY III (NURSES AND PIP IDENTIFICATION)

The study included 396 patients. The median age was 43 with an interquartile range of 30-56. The primary psychiatric disorder was schizophrenia (and other psychotic disorders). There was substantial comorbidity with 123/396 (31%) of the patients having one or more somatic conditions. The most frequent comorbidity was cardiac disease. There were no notable differences across the participating bed units indicating a successful selection of bed units that matched regarding patient diagnosis and age categories.

5.3.1. POTENTIALLY INAPPROPRIATE PRESCRIPTIONS

The SCPPs reviewed 396 patients and 2625 prescriptions comprising 1894 regular prescriptions and 758 PRN prescriptions. The medication reviews by the SCPPs showed that 66% (262/396) of the patients were prescribed at least one PIP.

Table 5-4 shows the primary outcomes of the scenario of potential improvement had all PIPs identified by SCPPs and nurses, received the relevant alterations. There was not a statistically significant DID in the mean number of PIPs per patient, between the control and intervention bed units. Additionally, the potential reduction of 11.8 percent point in the proportion of patients prescribed ≥1 PIP in the intervention bed units was not a statistically significant reduction. There was almost

no variation in the proportion of patients prescribed ≥1 PIP in the control bed units when comparing the baseline period and the intervention period.

Table 5-4. Potential improvements in number of potentially inappropriate prescriptions (PIPs) had all PIPs identified by seniour clinical pharmacology physcians and nurses been altered relevantly.

		Baseline period	Intervention period	Difference, 95% confidence interval	p-value
Mean number of PIPs per patient (±SD)	Interventional bed units	1.69±1.79	1.55±2.00	0.14 (-0.47-0.76)	0.30
	Control bed units	1.84±1.99	1.92±2.34	-0.09 (-0.72-0.54)	0.92
	Difference-in-difference (95% confidence interval)			-0.23 (-1.07-0.60)	0.59
Number of patients prescribed ≥1 PIP (%)	Interventional bed units	38 (65.5)	65 (53.7)	0.61 (0.32-1.17)	0.14
	Control bed units	48 (65.8)	95 (66.0)	1.01 (0.56-1.83)	0.97
	Difference-in-difference (95% confidence interval)			0.61 (0.25-1.46)	0.26

SD: standard deviation.
Differences in means were compared using a Wilcoxon rank sum test, and differences-in-difference was estimated with a linear regression model.
Odds ratios for the intervention and control bed units comparing before-and-after was estimated using logistic regression and difference-in-difference was estimated by the OR for the coefficient for interaction between groups (intervention bed unit/control bed unit) and time (before/after) in a logistic regression model.

Nurses' identifications of PIP

The nurses in the study reviewed 121 patients who were prescribed 756 prescriptions, consisting of 548 regular prescriptions and 208 PRN prescriptions.

The nurses identified 51% (62/121) of patients as having one or more PIPs with a moderate interrater reliability between nurses and SCPPs. The overlap between the nurses and the SCPPs' identifications of PIPs totalled 38 PIPs equalling 17% of the SCPPs' identifications of PIPs. The nurses identified 13 potentially serious and five potentially fatal PIPs in the '*interaction between drugs'* category. In total, they identified 38% (24/64) of all PIPs identified by the SCPPs in the '*interaction between drugs'* category. The nurses' second most common finding was '*omission of indication'* (n=20), overlapping with only four PIPs (13%) identified by the SCPPs in the same category. When only PIPs overlapping with SCPPs' assessments were included, potentially fatal PIPs were identified in the categories '*interaction between drugs'* (n=5) and '*interaction between drug and disease'* (n=1).

Secondary outcomes

Physicians altered or wrote prescriptions for 25 patients in response to nurses' observations. The nurses' observations covered 11 categories of PIP and the physicians altered or wrote prescriptions in 10 of the 11 categories. The physicians altered or wrote most prescriptions in the category '*interaction between drugs'* and '*omission of indication for treatment'*. Only in the category '*interaction between drugs'* did the physicians alter prescriptions assessed to be potentially harmful by the SCPPs. The proportion of PIPs altered or written by physicians in response to nurses' observations during the intervention was 34% (95%CI 26.4-42.9). Only 17% (95%CI 7.6-30.8) of the PIPs identified by nurses and responded to by physicians, were also PIPs identified and assessed for severity by the SCPPs.

5.4. STUDY IV (NURSE-PHYSICIAN COLLABORATION)

5.4.1. THEMES AND SUBTHEMES

The thematic analysis of the focus groups revealed three themes which were divided into subthemes, as illustrated in Table 5-5. The themes covered both barriers and promoters for NPC, and also the circumstances with potential for being both a barrier as well as a promoter (named 'Janus circumstances' after the two-faced Roman God).

Barriers to nurse-physician collaboration

The feeling of not being heard

Specific barriers mentioned by nurses were of an emotional character, for example the feeling of being ignored and not heard resulting in resignation to the situation.

Table 5-5. Themes and subthemes.

Theme	Subtheme	Supporting quotes
Barriers to NPC	The feeling of not being heard	When I tried to question something, I would not get very far. They (the physicians) are rarely rude. They just sort of ignore you and then I withdraw from commenting on medications (a couple of other nurses broke in and supported this view by saying they had the same feeling) – *Focus Group 2, Participant 1*
	Disputes between physicians	Sometimes the nurses get caught in the middle if physicians disagree on the medication and then it is easy to lose the general idea of what to observe and report. It becomes random – *Focus Group 1, Participant 1*
Promoters for NPC	Physicians inviting nurses to collaborate	When physicians review the medication before discharge and take the initiative to involve us, and we talk and review together…the nurses will often be able to tell something extra about the patient's use of medication which is not described in the patient record – *Focus Group 2, Participant 2*
	Access to physician	Whenever I get the chance to speak to the physician myself, I will. I get a much better understanding of the patient's entire medical situation, and the physician receives updated information about the patients' medications. The patients talk to us [nurses] in a different way, and I can better help the patients express their experiences and needs when we are all there. It is the best way – *Focus Group 1, Participant 9*
The Janus circumstances: can be both barriers and promoters	Having experience from somatic care	The culture is so different between physicians and nurses [in psychiatry]. However, you let yourself be lulled into apathy here. I do not think too much about it anymore, but it used to bother me terribly, that so many patients had somatic comorbidity and it received next to none attention – *Focus Group 1, Participant 3*
	The way rounds are organised	1. It offers more responsibility and more ownership when you go rounds on your own patients and discuss whatever is relevant for the patients' medication regime. The information you can offer the physician becomes more nuanced – *Focus Group 1, Participant 8* 2. The person who walked the ward round had not seen that the patient used ibuprofen, had abdominal pain, and black stools - and any assistant knows that black stools and low haemoglobin equals a phone call to the

	physician – and, well, it went terribly wrong – didn't it? [addressing colleagues from her own ward]. The way we go rounds is antiquated'. – *Focus Group 2, Participant 1*
The way nurses perceive own medication competencies	1. If we want to do more of this… recognising when the medications are doing the patients no good… we need annual courses like we have on handling conflicts and cardiac arrest – *Focus Group 2, Participant 1*
	2. I mean, if the medication is a problem, it was created by the prescribers. The monkey should not be passed onto the nurses - *Focus Group 2, Participant 3*

Disputes between physicians

In addition, encounters involving disagreements between physicians were described as barriers which influenced the nurses' ability to focus on effects and side effects of patients' individual pharmacotherapies. The disputes between physicians about patients' medications left nurses worried that medication safety was jeopardised through non-systematic observations.

Promoters for NPC

Physicians inviting nurses to collaborate

Promoters for NPC described by the nurses involved experiences where physicians had initiated collaboration and took initiative to discuss medication plans. The nurses linked 'good communication' in the NPC with including the nurses' observations and opinions in the conversation. Concurrently, the nurses described how physicians who were explicit in their expectations and appreciation within the NPC added positively to the nurses' professional competencies, as well as their job satisfaction.

Access to a physician

Being able to talk to and discuss medications directly with a physician was described by the nurses as providing an opportunity to learn about medications and pharmacotherapy from the physician. Access to the physician was also seen by the nurses as a way to increase knowledge about medication and treatments to improve the broader management of treatment and care for the patients.

The Janus circumstances: can be both barriers and promoters

Having experience from somatic care

Nurses with extensive experience in medical, surgical and intensive care unit settings expressed two perspectives on NPC. Firstly, there was the perception that a reluctance to address somatic issues in psychiatry curbed their opportunities to use

their experience actively in the clinical setting. Secondly, the somatic experience was also seen as a qualification that could facilitate more holistic patient care.

The organisation of ward rounds

The nurses saw ward rounds as a necessity and important for the NPC, however, the framework within which the ward rounds were processed in the two bed units sparked different views. One ward had organised their ward rounds so that physicians would seek out the contact nurse and they would see the patient together. This was, without exception, seen as a propitious procedure. The other unit had organised their ward rounds so that one senior nurse, usually the same one, handled the ward round with the physicians, and the nursing input consisted of notes from the nurses on the floor to this senior nurse about what the physician needed to attend to. All nurses from this bed unit considered this type of ward round unsuitable in contemporary nursing. A few nurses also remarked that it produced a feeling of hierarchy between the nurse doing rounds and nurses on the floor.

The way nurses perceive their own medication competencies

All nurses perceived their medication competencies as insufficient and there was a general aspiration to improve their knowledge of pharmacology and medication optimisation. One nurse suggested a formal approach similar to annual courses already in place at the hospital in which the nurses were employed. The nurses also saw their role as central to the patients' medication adherence as well as in offering support and advice in situations where the patients had questions about medication or were reluctant to take the prescribed medications. However, the nurses also saw room for improvement in their counselling of patients, due to their lack of knowledge. All nurses agreed with, and consistently encompassed the act of observation of effects and side effects as part of nursing. Nevertheless, there was also hesitancy among some of the nurses in taking on medication optimisation through NPC, as this was seen as additional work not related to nursing.

CHAPTER 6. DISCUSSION

6.1. PRINCIPAL FINDINGS

This thesis investigated errors in the medication process, PIPs, nurses' potential for reducing the prevalence of PIPs, and finally nurses' perceptions of collaborating with physicians on medication optimisation in psychiatry.

The findings contribute to knowledge about errors in the medication process in psychiatric bed units. The study concluded that patients in psychiatry, during the medication process, are exposed to errors in to a degree similar to that found in somatic hospitals. Additionally, the potential clinical consequences for psychiatric patients are serious and similar to those identified by researchers in somatic hospitals.

PIPs are also frequent and affect more than half of all psychiatric patients admitted to psychiatric hospital. A significant proportion of PIPs has the potential to harm patients and in some cases may even prove fatal. Drug-drug interactions were the main category of PIPs. The findings also indicated somatic illness and polypharmacy as risk factors for PIPs.

Nurses might be an unrecognised resource in preventing and mitigating PIPs in terms of what PIPs the nurses identify and report to physicians and to what extent. However, the study also demonstrated that PIPs changed by physicians based on nurses observations not necessarily correspond with the findings of PIPs by SCPPs in the same population. The effect of the nurse-led intervention was limited and not statistically significant when comparing results before-and-after.

The characteristics of NPC, from the nurses' perspective, partially explain the limited effect of nurses identifying and reporting PIPs. Nurses described barriers, promoters and certain circumstances in which both negative and positive outcomes was a possibility. Barriers included the individual nurse's feeling of not being heard and doubt in the correctness of medications as consequence of physicians' disagreements. Promoters included physicians actively engaging in collaboration and the nurse having an actual possibility of reviewing the patient together with a physician. The ambiguous circumstances involved, among other, when nurses had somatic experience. The nurses described somatic experience as either favourable or as a source of frustration rooted in feeling helpless due to a perception, on the part of the nurses, of a disinclination to treat physical illness in psychiatric hospitals. The ambiguous circumstances also included the organisation of rounds on the bed units as well as the nurses' self-perceived medication competencies.

6.2. COMPARISONS WITH EXISTING LITERATURE AND METHODOLOGICAL CONSIDERATIONS

6.2.1. STUDY I (ERRORS IN THE MEDICATION PROCESS)

There were errors in 17% of all opportunities for error and trying to compare this error rate with existing literature will, at its best, be limited. Depending on the study question, the numerator can be an event or a time interval where the event or time interval in question also varies. Some examples from psychiatry are: 6.22 self-reports of error per 1000 patient days (all stages in the medication process) (17), 5.5 per month (all stages in the medication process) (131), 0.024 per prescription (the prescribing stage) (135), 0.82 per patient (132). These estimates do not allow direct comparisons.

Errors in the administration stage were the most frequent error type. Only a few studies have investigated administration errors in psychiatry. In this present study, administration errors constituted 142/340 (42%) of all errors. The relatively high proportion of administration errors is in contrast to other studies, as one study reported 10% of all medication errors as administration errors and another study of elderly psychiatric patients reported 25.9% of all errors as administration errors (77,131). Although the same denominator was chosen in the aforementioned studies, e.g. opportunities for error, the variation is most likely due to differences in error types in the administration stage and local guidelines on the administration of medication. Of all errors in the administration process, the clinical pharmacologists assessed 51% as potentially serious and 1% as potentially fatal. This is in contrast to Haw et al., who assessed that approximately 15% of identified errors in the administration stage had the potential for harming patients (77).

Discharge summaries comprised 10% (19/189) of all errors in the study. This finding cannot be compared directly to other studies due to methodological differences. However, in earlier studies, the correctness of discharge summaries has been poor (172) and rates of error up to 36% and 41% have been stated (165,173).

A Danish study also applying unannounced visits as a method of data collection stated that surgery and psychiatry had the highest rates of dispensing errors. This present study applied two methods showing a 10% difference in the proportion of error. It is possible that the two different error rates in the dispensing stage in this present study (9/324 (3%) and 9/67 (13%)) stemmed from the two different methods of detecting errors in that stage, but most likely from a dependency in data which arose from the few nurses and nurses' assistants participating. Other studies, have found error rates ranging from ≈2% to 5% (75,165).

In this present study, an error was identified in 4% of all opportunities for error in the prescribing stage. However, only the communicating (writing) of a prescription and not the decision-making related to the prescription - was included. As with all other measurements of prevalence in the medication process, the prescribing stage is challenged. Nonetheless, our finding is supported by a systematic review from 2009 where a median error rate of 7% was established (174). The systematic review also underlined the difficulty in measuring the severity of prescription errors (174). Most of the prescription errors in this present study were of the type '*lack of PRN regime*' where the physician had prescribed PRN medications without specifying a maximum dosage per day.

Methodological considerations

The majority of studies on errors in the medication process have, so far, primarily been conducted in somatic hospital settings with only a few studies including a psychiatric population. This present study provides an important contribution to the current knowledge about errors in the medication process in psychiatric hospitals due to methodological choices. On the one hand, the study sample was small - only 67 patients were included - which is thus a potential weakness of the study. On the other hand, using 'opportunity for error' as a denominator provides the strength of a larger sample. The strength of the study is the choice of method for detecting errors in each stage of the medication process. For each stage, the most sensitive method was applied (51,52,175) and the potential bias in observational studies was identified and quantified through the unannounced control visit. However, this was not completely successful, as the majority of errors was associated with one nurse assistant, leading to a diminished reliability when comparing with other hospitals or settings where the dispensing of drugs is undertaken by the pharmacy. The study appears to have good internal validity, but was carried out in a single university hospital with a limited generalizability as consequence. Nevertheless, other psychiatric hospitals might face similar issues with medication safety and –in comparison with somatic hospitals – may be equally challenged in improving the quality of the medication process.

Study I included prescription errors related to the communicating of the prescription, but not the decision-making part of prescribing and in the process of assessing prescription errors related to the communicating of prescriptions, the research group identified a number of potentially inappropriate patterns of prescribing which led to the design of Study II.

6.2.2. STUDY II (CHARACTERISTICS OF PIPS)

This study reported that 59% of all patients admitted to a bed unit had one or more PIPs which is supported by a systematic review reporting a prevalence of PIPs for the elderly, ranging from 21.4%-79.0%. Their finding represents a wide range and one may speculate whether this represents local patterns of prescribing as the

criteria used in the detection of PIPs are the same. The finding of the use of combination therapy with antipsychotics or antipsychotic polypharmacy (the use of one or more antipsychotics) as the most frequent PIP is hardly surprising as the practice of antipsychotic polypharmacy has been extensively investigated, cautioned against except for certain specific circumstances, and found to be frequent worldwide (176). Another finding in this present study was the use of combination therapy with antipsychotics and antidepressants which several times was assessed as potentially harmful. Studies have investigated major depressive disorder (MDD) and there is partial evidence for the augmentation of treatment with second-generation antipsychotics to antidepressants, however this is also accompanied by a higher risk of adverse events (177,178). Older studies demonstrated polypharmacy and somatic illness as predictive factors of PIP (179,180). This present study confirmed the same to be the case in a psychiatric population and this is emphasised by a study of psychiatric comorbidity on 30-day all-cause readmissions after heart failure, acute myocardial infarction and pneumonia (181). The latter study found a significantly higher readmission rate for patients with psychiatric comorbidity compared to patients without comorbidity. In the present study, patients receiving five or more medications had an almost two and a half times higher risk of potentially serious or potentially fatal PIPs than patients receiving less than five prescriptions. Additionally, having one or more somatic diagnoses yielded an almost two times higher risk of potentially serious or potentially fatal PIPs than patients with no somatic diagnoses. Age was not a statistically significant predictor of PIP but this might be due to psychotic disorders being the most prevalent mental disorder in young patients and the consequential treatment with antipsychotics.

When comparing the findings from this study and those of a literature review regarding what are considered to be high-risk drugs, there were several drugs in common (182). Some examples are methotrexate, NSAID, opioids, acetylic salicylic acid, other anticoagulants, beta-blockers, antibiotics, sulphonylureas, antipsychotics, and antidepressants. Consequently, what are considered high-risk drugs in somatic hospitals are also prevalent in psychiatry and should receive equal attention when prescribed for patients with psychiatric disorders.

Methodological considerations

There are several strengths to this study. To the author's knowledge, this is the first study to apply medication reviews carried out by clinical pharmacologists in newly admitted psychiatric patients. The clinical pharmacologists had extensive pharmacological expertise as well as clinical knowledge of psychiatric patients and applied this in the detection of PIPs and the assessment of potential clinical consequences. The aim was a detailed picture of the appropriateness of prescribing for psychiatric patients at the time of admission, and where other studies have applied explicit criteria, this study applied an implicit approach. The explicit criteria is tantalising from a researchers point of view but not satisfactory, as not all

possible PIPs can be listed and will not necessarily apply to all individuals (90,183). The advantage of the implicit approach is the holistic viewpoint, in which all the patients medications are included along with the patient's preferences, best available evidence and the individual traits of knowledge and experience of the clinician (90,103). However, the implicit approach where only one clinical pharmacologist carried out the medication review and assessed PIPs for potential clinical consequences might introduce a less reliable result. Assessment by consensus has been used in one of two forms: a) agreement among peers without preset criteria; and b) a process such as the Delphi technique until consensus was reached (183). This is not without problems either, as experts can agree and yet be wrong (184).

In Study II, it was concluded that there was a need to improve physicians' knowledge of pharmacology as well as nurses' knowledge of medication safety issues. Study III emerged in recognition of nurses' central role in handling medication.

6.2.3. STUDY III (NURSES AND PIP IDENTIFICATION)

In this study, medication reviews were also used to detect PIPs following the same procedure as in Study II. However, this present study found a higher prevalence of PIPs (66% of patients) than the prevalence of PIPs identified in Study II (59% of patients). In a recent study, in older patients admitted to psychiatric hospital, researchers found, that 47% and 79% of all patients had potentially inappropriate medications (106) using Beers Criteria 2012 (185) and STOPP (186), respectively. These findings support this present study where 66% of the patients had one or more PIPs.

The nurses found 38/224 (17%) of all PIPs identified by the SCPPs in the same sample. This is not a result directly comparable to other studies, as the finding is one of the first attempts to quantify to what extent and within which categories nurses identify PIPs in psychiatric patients. Both nurses and SCPPs identified the majority of PIPs in the category 'interaction between drugs' where the nurses identified 24/64 (38%) of PIPs also identified by the SCPPs. In a study from Sweden, where nurses identified drug-related problems (DRPs), it was found that 22% of the identified DRPs were potential drug interactions (23) as opposed to the 24/64 (38%) identified in this present study. The Swedish study based the data collection on a tool screening for symptoms in the patient, whereas this present study based the data collection on the appropriateness of prescriptions. Thus the prevalence in the Swedish study might be lower as the explicit criteria of the screening tool is only sensitive to patients already presenting with ADRs and does not apply to all prescriptions for all patients.

Nurses and SCPPs identify and observe PIPs based on two different foundations. Nurses use guidelines, knowledge about the patient, whatever pharmacological training they have received, occasional self-studies, and will ask colleagues for advice (153,187) whereas the SCPPs in this study strictly applied evidence based guidelines and clinical pharmacological reasoning.

Physicians' acceptance rate of changing medications, according to pharmacists' suggestions, for instance, has been found to be moderate (188,189). Physicians may be more likely to accept advice or suggestions on medication from another physician and are, as mentioned before, less inclined to do so if the medication counselling is given by a pharmacist (190). In a survey of physicians' perceptions of medication counselling, 30% of the physicians found it of major importance that the person providing medication counselling was part of the team, but only 18% found it to be of major importance that the person providing the medication counselling was a pharmacist (190). Data does not tell whether a person who is 'part of the team' could be a nurse, seen through the eyes of the physician. Nevertheless, physicians in the present study changed or altered prescriptions for 47/137 (34%) of the PIPs identified by nurses. However, only 8/47 (17%) of prescriptions altered by the physicians were also prescriptions identified by the SCPPs.

All errors are important in medication research, as even insignificant errors indicate flaws in the medication process which again might result in harm given other circumstances (27). The nurses identified potentially serious, and even potentially fatal PIPs, but also PIPs of minor clinical importance indicating that nurses' achievements in medication-related activities, such as evaluating prescriptions, ensuring patient adherence to medication, and observing effects and side effects of medication is an overlooked activity in need of future examination of their potential in this area.

Methodological considerations

There were several strengths in the study. The first of these was the pharmacology course where the nurses were trained to observe and identify PIPs in a consistent and systematic way. Second was the use of the SCPPs' medication review as the gold standard against which the nurses' observations were validated and third was the documentation of physicians' alterations to prescriptions in response to nurses observations of PIPs. Finally, the before-and-after design with a control group provided a baseline for observing any increase or decline in the prevalence of PIPs indicating if other factors influencing the prevalence of PIPs. The DID approach provided an estimate of the potential reduction in PIPs between the control and the intervention group controlled for permanent differences between the control and the intervention group (191). Bias from comparisons over time, because of trends, was also controlled (191). There were also limitations to the study. Prescribing patterns in the study only represented one study site, and thus generalisations must be made

with caution. The exactness with which one can measure PIPs is uncertain and will depend on the adopted approach (90). Randomisation and blinding were not feasible. Randomisation on the individual level was unsuitable due to the risk of educational bias between nurses on the bed units. Blinding was unsuitable due to the nature of the intervention. Additionally, there were no assessments of intra-rater reliability for the SCPPs; however, the interrater reliability between nurses and SCPPs for identifying a patient as having a PIP was assessed. Finally, the choice of SCPPs' medication reviews proved somewhat problematic as it produced the question of relevance and characteristics of the sizeable proportion of PIPs identified by the nurses and responded to by the physicians, which were, however, not suggested as PIPs by the SCPPs.

The nurses participating in Study III, also participated in the focus group interviews on which Study VI is based. The focus group interviews were carried out before the intervention period in Study III and have helped shed some light on some of the subsequent results in Study III.

6.2.4. STUDY IV (NURSE-PHYSICIAN COLLABORATION)

This study about nurses' perceptions of collaborating with physicians regarding medication optimisation for psychiatric patients, may explain aspects of the other studies on which this thesis rests. During the focus group interviews, nurses consistently talked about physicians who were initiators in NPC as 'good collaborators'. Surprisingly, they did not bring up nurses as facilitators for NPC. There is evidence indicating that positive NPC relationships bring about several beneficial outcomes for both patients, nurses, and physicians (121,126,192,193). The potential consequences of NPC relationships for patient outcomes and job satisfaction are scarcely investigated in psychiatry. Some nurses in this present study spoke of 'access to the physician' as something difficult to obtain yet a prerequisite for discussing and passing on valuable information about their patients. Physicians were seen by the nurses as an opportunity for increasing knowledge about medication and treatments to improve their nursing competencies. Kramer and Schmalenberg have performed many studies investigating nurse-physician relationships, and an excerpt of their work is the suggestion of five types of nurse-physician relationships. The five types of relationships are '*the collegial'* (described as **equal** trust, power, and respect), '*the collaborative'* (described as **mutual** trust, power, and respect), '*the student/teacher'* (where either nurse or physician can be teacher and the other willing to listen and learn), '*the friendly stranger'* (described by the formal exchange of information and a neutral tone), and '*the hostile/adversarial'* (described by anger, verbal abuse, threats, or resignation) (194). Nurses in the present study primarily described collaboration in terms best characterised by '*the student/teacher relationship'* and '*the friendly stranger relationship'*. One may speculate that the results from Study III where physicians responded to a modest proportion of PIPs identified by the nurses, of which an even

smaller proportion were identical to the SCPPs findings, is a manifestation of the type of collaboration taking place. The picture is not clear, as the physicians have displayed a willingness to alter prescriptions based on nurses observations, however only a small proportion of prescriptions altered were also identified as PIPs by the SCPPs.

A 'magnetic' hospital is a hospital where nurses are consistently attracted, retained and deliver high-quality care. The environment in a hospital is said to be magnetic when attributes considered **important** to job satisfaction and productivity of quality care by staff nurses, are also **present** (195). Though physicians tend to view collaboration less important than nurses (123,196), nurses' job satisfaction and perceptions of achieved quality in care for patients is closely linked to positive NPC relationships (193,194). The nurses in this present study also expressed the viewpoint that positive NPC on medication optimisation was rewarding in terms of achieved quality and job satisfaction. Additionally, it also became clear that the nurses' experience of 'a magnetic environment' was linked to the organisation of the collaboration between physicians and nurses, e.g. ward rounds.

The focus group interviews gave rise to some interesting reflections by nurses who had somatic experience and were now employed in the psychiatric bed units. The findings indicated that nurses with somatic experience perceived some differences in NPC in psychiatric hospitals compared to somatic hospital settings. These nurses with somatic experience described the NPC in less favourable terms in psychiatry. They would use wording consistent with collegial and collaborative nurse-physician relationships about their work in somatic settings and while describing their current situation with wording consistent with the friendly stranger relationship or even, in a few cases, a hostile/adversarial nurse-physician relationship. Whether this expresses that nurses experience more satisfactory NPC regarding medication optimisation in somatic hospital settings than in psychiatric hospital settings remains to be studied. It must be considered that the nurses, with the wisdom of hindsight, recalls the work conditions in somatic hospitals as being better than what they actually were.

The nurses considered the ward rounds to be the primary point of contact with physicians, and findings in the present study indicate that the setup of ward rounds plays a vital role in how nurses view their opportunities for collaborating with physicians regarding medication optimisation.

There were two primary perceptions of the nurses' self-perceived competencies and responsibilities in terms of medication optimisation. The first perspective was nurses being competent and central in communicating with patients about medication. The other perspective was more unforthcoming where nurses questioned the extent and relevance of their knowledge to be good collaborative partners to physicians. The most cautious nurses questioned whether nurses have

any role in medication optimisation and suggested that responsibility for appropriate medication rests solely with the physician. The nurses' reflections also touched on the experience of not having enough knowledge. Sometimes the nurses would handle, and administer medications of which they knew nothing, except for what could be looked up online or what could be found in the patient's information. This finding is supported by Happel et al., who described that nurses report knowledge sources such as the Internet, using information pamphlets meant for patients, consulting pharmacists and using drug representatives as a source of education (153). Another study also found that nurses expresses limited knowledge about pharmacology while seeing knowledge about pharmacology as essential for clinical practice (197). However, a more recent cross-sectional, Swedish study demonstrates that nurses self-perceived competencies and pharmacovigilant activities are significantly higher after receiving university-based pharmacology courses than if they had not participated in such courses (198).

Methodological considerations

The purpose of the study's design was to describe themes emerging from a specific site (199), not to ensure or evaluate whether the study's results were representative for nurses employed in psychiatric bed units. Due to the nature of focus group interviews, the study had some inherent weaknesses. Firstly, focus groups will often consist of participants who are not familiar with one another to prevent participants being inhibited or subservient due to characteristics with-in the group (169,199). This present study included, in each focus group, nurses who knew each other from their current workplace and nurses who were not familiar with each other. This choice was made because the present study links to the context in which Study III was carried out. The combination of everyday colleagues and colleagues from another bed unit opened up the possibility of addressing issues that might not be touched upon on a day-to-day basis in the individual bed units but also to investigate differences between two seemingly uniform bed units. There is always the risk of the group dynamics influencing the individual to support the viewpoint most acceptable to the group (170). However, all nurses spoke at one or more points during the interviews. The phrasing of questions and conducting of data analysis have obvious potentials, for influencing outcomes. Attempts to avoid this included an independent researcher, who was not involved in the study in any way, checking correctness of transcribing, and consensual discussions between the researchers throughout the process of developing relevant themes. Data saturation might not have been met, due to the evident limitations in having only two focus groups. This excludes the necessary iterative process (200). Conversely, identical themes emerged from both focus groups and within group saturation on themes were accomplished (199,200).

CHAPTER 7. CONCLUSION

The purpose of this thesis was to investigate the extent and nature of errors in the medication process, PIPs, and nurses' potential role in improving the quality of prescribing for psychiatric patients.

The objective in Study I was to evaluate the prevalence, types, and potential clinical consequences of errors in the medication process in psychiatric wards. The study demonstrated errors as a real and comprehensive problem in psychiatric hospitals with most errors occurring in the administration stage. Additionally, establishing a patient's identity before administration of medication was the most frequent type of error. Using a definition that discriminates errors from medication errors by the potential for harm to the patient revealed that only a small proportion of errors in the medication process appears to be potentially fatal. However, the majority of errors in the administration stage were assessed as potentially serious.

The objective in Study II was to evaluate the prevalence, types, and predictors of PIPs as well as the severity of potential clinical consequences. The study revealed PIPs to be frequent with drug interactions as both the most frequent PIP but also the most important category in terms of potential harm or fatality to patients. It was also demonstrated that polypharmacy and the presence of somatic comorbidity were factors predictive of PIPs.

The objective in Study III was to examine the characteristics, magnitude, and potential effect of pharmacologically trained nurses' systematic review of medication records on the appropriateness of prescribing for newly admitted psychiatric patients. The study did not show any statistically significant potential improvement in PIPs, either in the mean number of PIPs per patient or the number of patients prescribed ≥1 PIP. Nonetheless, in the study population, nurses identified PIPs also identified by SCPPs and assessed by SCPPs to be potentially harmful to patients. Physicians responded to some of the nurse-identified PIPs, but assessed the majority of nurse-identified PIPs as not clinically relevant.

The objective in Study IV was to explore how nurses perceive collaborating with physicians on medication optimisation for psychiatric patients. The study addressed nurses' views and perceptions of medication optimisation as a result of NPC. The limited success in Study III might be partially explained by the findings in Study IV. The nurses primarily described relationships characterised by a '*student-teacher relationship'* and a '*friendly stranger relationships'*. Study IV raises expectations that skilled and confident nurses can provide physicians with precise and adequate information to share responsibility for medication optimisation and can provide

patients with high-quality information and support their adherence to appropriate medications.

CHAPTER 8. FUTURE PERSPECTIVES

Much research and effort has been spent on definitions and classification of medication errors, including the definitions used in this thesis (26,29–31,201). Many researchers have also tried to establish frequencies of medication errors using a variety of methods (17,40,77) and the special challenges facing psychiatry in this regard have also been touched upon (16,203). Some examples are TDM and off-label prescribing. However, the reality is most likely that an exact frequency of medication errors will remain unknown (27), as both method of detection and terminology can affect outcome (27,31). Yet, it is crucial to continue monitoring errors and medication errors to determine where improvement interventions are needed.

As the exact frequency of medication errors will remain unknown, so will the exact frequency of PIPs remain unknown, as 'appropriateness is in the eye of the reviewer' and formed by evidence and the individual knowledge and experience of the clinician (89). However, the presence of PIPs is indisputable and in addition, an issue that needs to be addressed sensitively and rationally to prevent patients from suffering unnecessary doubt or anxiety about their medication and to keep the debate nuanced and based on evidence.

Several times during the research for this thesis, physicians have asked: '*but did you identify any patients harmed by PIPs*?'. On the one hand, there were no patients identified who had suffered any harm at the time, which is hardly surprising as the study design is cross-sectional and only seeks to measure the presence of PIPs – not its actual consequences which requires a prospective design. On the other hand, the question of whether PIPs actually harm patients is valid – yet, unanswered. With that established, it is necessary to mention that during the data collection period, the research group was acquainted with a handful of incidences suspected to be medication-related. In the future, large-scale studies that prospectively investigate the consequences of PIPs should be considered.

The present thesis also addressed nurses' role in medication safety in psychiatry. The findings in Study III indicate that systematic efforts to improve nurses' clinical reasoning about the safe use of medications and their observations of effects and side effects provides part of the foundation on which balanced prescribing rests. The potential for improvement has been quantified. However, what constitutes a clinically relevant PIP to a physician versus an SCPP, remains to be investigated. If nurses are to make a positive difference in improving the quality of prescribing for psychiatric patients, they can only do so in collaboration with physicians.

The results from Study IV indicate that the different types of nurse-physician relationships described in the literature (193,204) also exist in psychiatric hospitals. The results also indicate how organisational structures, for example ward rounds, have an impact on the quality of these nurse-physician relationships. Additionally, prospects are that nurses can improve their skills on the clinical observation gap between physician and patient by bonding nursing and medical knowledge in terms of NPC on medication optimisation, however, this remains to be examined further in the future.

Nurses are an already existing resource which, to a degree and in collaboration with physicians, offers hope for improvement. However, realising the potential for nurses to improve medication quality and safety in psychiatry, requires leadership and an organisational will to give room to NPC. NPC implies that interprofessional committees include both nurses, physicians, and other relevant professions, and regular and interprofessional reviewing of patients. Nurses' work, including rounds on the bed units, must be planned with the optimisation of NPC in mind, including regular pharmacology and medication safety education for the nurses. Decision-makers must realise that the abovementioned potential benefits cannot be realised without the will to make organisational changes.

Finally, the physicians' perspective on NPC about medication optimisation was not investigated in this thesis. Shekelle et al. point to teamwork, leadership, and patient safety culture as some of the contextual factors impacting on the success with which a patient safety intervention can be implemented and sustained (159). Therefore future studies that focus on the physicians' views and perceptions of NPC in terms of medication optimization, but also medication safety in general are needed.

The finishing remark is given to an American nurse, who as early as 1939, in The American Journal of Nursing (205) wrote:

'Nurses are in a peculiar and often difficult situation in carrying out the orders of physicians. Friction may arise where it could be avoided if both nurses and doctors would remember that the only thing which really matters is the welfare of the patient, not that one group gives, and the other carries out the orders'.

Margene O. Faddis, RN, 1939.

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APPENDICES

Appendix A. Error types in the medication process (Study I)

Study I. (Errors in the medication process).

Prescribing		Dispensing	Administration
Decision-making	**Communication**		
Allergy	Allergy information	Ambiguous information on label	Contamination
Calculation error	Decimal place error	Incompatibility errors	Incompatibility errors
Interaction drug and disease	Ambiguous drug name	Contamination	Extra dose
Interaction between drug and laboratory test	Ambiguous drug prescription	Expired drug	Lack of control of patient identity
Drug to drug interaction	P.r.n. prescription without a maximum limit	Omission of dose	Omission of dose
Extra drug	P.r.n. prescription without a minimum dose limit[a]	Omission of documentation of drug dispensing	Lack of documentation of the drug administration
Omission of a drug prescription	Omission of indication for treatment including p.r.n prescriptions	Omission of control of the drug prescription	Lack of control of agreement between administered drug and prescribed drug
Wrong concentration	Illegible handwriting	Substitution error	Unordered drug
Wrong drug form	Omission of rate of infusion	Unordered drug	Wrong dose
Wrong dose	Discrepancy between dose intervals	Unordered electrolyte[a]	Wrong patient
Wrong dosing interval	Discrepancy between indication of dose	Wrong concentration	Wrong dosing interval
Wrong drug	Wrong transcription	Wrong drugform	Wrong rate
Wrong route of administration		Wrong dose	Wrong route of administration
Wrong duration of treatment	Omission of dose[a]	Extra dose	Wrong technique
Wrong strength/unit	Omission of strength per unit[a]	Wrong strength per unit	Wrong time
Omission of ordering laboratory tests	Omission of documenting the effect of drug treatment[a]	Wrong dilution fluid	Omission of documentation of side effects of the treatment
	Omission of drug formulation[a]		
	Omission route[a]		
	Omission of dosing interval[a]		
	Omission of treatment time[a]		
	Omission of signature[a]		
	Omission of date[a]		

[a]*These error types are all included in the error type 'Ambiguous drug prescription'.*
Adapted from Lisby M, Nielsen LP, Brock B, et al. How should medication errors be defined? Development and test of a definition. Scand J Public Health. 2012, by permission of the Nordic Society of Public Health.

Appendix B. Categories of potentially inappropriate prescriptions (PIPs) (Study II and III)

Study II and III.

Categories of potentially inappropriate prescriptions (PIP)	Description
Allergy	The patient develops an adverse reaction (AR) (18) caused by an abnormal immune response to a medication.
Omission of indication for treatment	There is inadequate documentation in the EMR[a] of the indication for treatment.
Drug dosage too low	The dose is too low to achieve the goal of therapy and/or below the recommended minimum dose in the European Public Assessment Report (EPAR) for the drug (http://www.ema.europa.eu/ema/). If the drug is not evaluated by the European Medicines Agency (EMA) then the product resume supplied by the Danish Medicines and Health Authority (https://sundhedsstyrelsen.dk/da/medicin/find-medicin/produktresumeer) has been applied.
Drug dosage too high	The dose is above the recommended maximum dose in the EPAR for the drug (http://www.ema.europa.eu/ema/). If the drug is not evaluated by the European Medicines Agency (EMA) then the product resume supplied by the Danish Medicines and Health Authority (https://sundhedsstyrelsen.dk/da/medicin/find-medicin/produktresumeer) has been applied.
Interaction between drugs	The pharmacologic result of two or more drugs interacting both pharmacokinetically and pharmacodynamically.
Interaction between drug and disease	The drug has the potential to interact with the patients' underlying illness(es) and cause harm to the patient.
Duplicate drug	The duplicate prescribing of the same medication product or the same therapeutic medication class.
Inappropriate dosing interval	The time interval between doses are too short or too long to achieve an appropriate clinical outcome.
Inappropriate dosing time	The drug has been prescribed for an inappropriate time of day.
Inappropriate drug form	The drug has been prescribed in a form inappropriate for the purpose or inappropriate for the patients' condition.
Inappropriate route of administration	The drug has been prescribed to be administered via another route than the first choice according to guidelines and without documentation for the relevance of the route of administration.
Inappropriate duration of treatment	The duration of therapy is inappropriate according to guidelines.
Omission of a potentially useful medication	The patient is eligible for drug therapy to treat an existing medical condition or reduce the risk of developing a medical condition. This assessment should be based on current guidelines.
Other	E.g. omission of relevant Therapeutic Drug Monitoring or ECGs.

Appendix C. Registration form for clinical pharmacologists (Study II and III)

Study II and III.

Registreringsskema: Potentially Inappropiate Prescribing

Bedømmer ID (LPN=0, BKP=1) (*marker hvem du er*)

Patientens CPR-nummer:

Patient ID:

1. Relevante blodprøver: *(skriv nedenfor)*

Nyretal (e-GFR, crea):

Levertal (ALAT, INR):

S-Elektrolytter (Na, K):

2. Kategorier af PIP (potentiel uhensigtsmæssig ordinering) samt klassificering af potentielle konsekvenser

Ved angivelse af PIP skal følgende kategorier anvendes:

0. *Ingen identificerede PIP*
1. *allergi*
2. *indikation (er der indikation for lægemidlet?)*
3. *dosis for lille*
4. *dosis for stor*
5. *interaktion mellem lægemiddel og sygdom*
6. *interaktion mellem lægemidler*
7. *dobbeltordination*
8. *uhensigtsmæssigt doseringsinterval*
9. *uhensigtsmæssig doseringstidspunkt*
10. *uhensigtsmæssig lægemiddelform*
11. *uhensigtsmæssig administrationsvej*
12. *uhensigtsmæssig behandlingsvarighed*
13. *POM(potential omission of medication) – indikation for et lægemiddel der **ikke** er ordineret*
14. *TDM (TDM mangler)*
15. *Andet*

Ved angivelse af potentielle kliniske konsekvenser skal følgende kategorier anvendes:

0. *potentielle non-signifikante kliniske konsekvenser*
1. *potentielle signifikante kliniske konsekvenser*
2. *potentielle alvorlige kliniske konsekvenser*
3. *potentielle fatale kliniske konsekvenser*

Registreringsskema: Potentially Inappropiate Prescribing

Bedømmer ID (LPN=0, BKP=1) (*marker hvem du er*)

Patientens CPR-nummer:

Patient ID:

2. (fortsat)

Potentielle uhensigtsmæssige ordinationer: (der *angives en kode for hhv. kategorier af PIP og potentielle kliniske konsekvenser jævnfør ovenstående kategorier. Ligeledes angives kort beskrivelse)*

Lægemiddelnavn(e)	**ATC-kode(r)**	**Kategori af PIP**	**Beskrivelse af PIP**	**Potentielle kliniske konsekvenser** **(Sæt kryds)**
				fatal □[3] signifikant □[1] alvorlig □[2] non-signifikant □[0]
				fatal □[3] signifikant □[1] alvorlig □[2] non-signifikant □[0]
				fatal □[3] signifikant □[1] alvorlig □[2] non-signifikant □[0]
				fatal □[3] signifikant □[1] alvorlig □[2] non-signifikant □[0]
				fatal □[3] signifikant □[1] alvorlig □[2] non-signifikant □[0]
				fatal □[3] signifikant □[1] alvorlig □[2] non-signifikant □[0]
				fatal □[3] signifikant □[1] alvorlig □[2] non-signifikant □[0]
				fatal □[3] signifikant □[1] alvorlig □[2] non-signifikant □[0]
				fatal □[3] signifikant □[1] alvorlig □[2] non-signifikant □[0]

Appendix D. Definitions of potential clinical consequences (Study I, II, III)

Study I, II and III

Category	Definition	Definition of keywords
Potentially fatal	Errors judged to imply a potential clinical risk for causing the death of the patient	Fatal refers to errors that could lead to the death of the patient
Potentially serious	Errors judged to imply a potential clinical risk of *injuring* the patient	*Injury* includes errors that would require active treatment to restore the health of the patient. A potentially serious error would lead to either permanent or temporary disability
Potentially significant	Errors judged to imply a potential clinical risk of being *inconvenient* for the patient – without causing any harm or injury	*Inconvenient* refers to unpleasant consequences of wrong dose/drug omission of dose/drug that could lead to pain, dizziness. It also refers to any monitoring of the patient such as extra blood tests, and measurements of blood pressure
Potentially non-significant	Errors judged to be without any potential clinical risk for the patient	Without clinical risk refers to errors that would not lead to any injury or inconvenience for the patient

The highlighted areas represent errors with the potential to harm patients.

Reproduced from Lisby M, Nielsen LP, Mainz J. Errors in the medication process: frequency, type, and potential clinical consequences.
Int J Qual Health Care. 2005, by permission of Oxford University Press

Appendix E. Programme for the nurses' pharmacology course (Study III)

Study IV

MODULOPBYGNING: FARMAKOLOGI OG HENSIGTSMÆSSIG MEDICINERING

Modul	Indhold	Underviser
Modul 1	8.00-8.30 **Kaffe og brød** 8.30-9.00 **Velkomst, baggrund og formål v/Ann.** 9.00-9.15 **Test af deltagernes viden** 9.15-10.30 **Lægemiddelområdet i Region Nordjylland. Organisering (herunder bla. RADS), vejledninger og kort om lovgivning. "On-line" hjælpesites, bla. Interaktionsdatabasen.** 10.30-10.45 **PAUSE** 10.45-12.00 **Generel farmakologi** 12.00-12.45 **FROKOST** 12.45-13.45 **Medicingennemgang og case arbejde** 13.45-14.00 **PAUSE og kaffe** 14.00-15.00 **Apoteket og farmaceutens rolle og rådgivning**	cand.scient.san, sygeplejerske Ann Lykkegaard Sørensen Overlæge Lars Peter Nielsen Overlæge Birgitte Klindt Poulsen Farmaceut Hanne Plet
Modul 2	8.00-8.15 **Kaffe** 8.15-9.15 **Erfaringer fra et studie af medicingennemgange hos psykiatriske patienter** 9.15-9.30 **PAUSE** 9.30-10.45 **Patientgruppe 1: Medicinsk behandling af mani, depression og bipolar lidelse - (Indikation, virkning, bivirkning, uhensigtsmæssige interaktioner og evt. seponering)** 10.45-11.00 **PAUSE** 11.00-12.00 **Patientgruppe 1 (fortsat)** 12.00-12.45 **FROKOST** 12.45-13.45 **Patientgruppe 2 : Medicinsk behandling af skizofreni (Indikation, virkning, bivirkning, uhensigtsmæssige interaktioner og evt. seponering).** 13.45-14.00 **PAUSE og kaffe** 14.00-15.00 **Patientgruppe 2 (fortsat)**	Ann Lykkegaard Sørensen Læge Jens Holmskov (hold 1) Læge René Ernst Nielsen (hold 2)
Modul 3	8.00-8.15 **Kaffe** 8.15-9.15 **Medicineringsfejl i det danske sundhedsvæsen** 9.15-9.30 **PAUSE** 9.30-10.45 **Patientgruppe 3: Medicinsk behandling af den voksne patient med ADHD - (Indikation, virkning, bivirkning, uhensigtsmæssige interaktioner og evt. seponering).** 10.45-11.00 **PAUSE** 11.00-12.00 **Patientgruppe 4: Medicinsk behandling af delir og demens - (Indikation, virkning, bivirkning, uhensigtsmæssige interaktioner og evt. seponering).** 12.00-12.45 **FROKOST** 12.45-13.45 **Behandling af diabetes hos den psykiatriske patient** 13.45-14.00 **PAUSE med kaffe** 14.00-15.00 **Behandling af diabetes hos den psykiatriske patient**	Cand.scient.san, sygeplejerske Ann Lykkegaard Sørensen Overlæge Ib Rasmussen Endokrinolog Agniezka Mulak-Król Overlæge Zoltan Kovacs
Modul 4	8.00-8.15 **Kaffe** 8.15-9.15 **Hvad er god sygeplejefaglig dokumentationspraksis?** 9.15-9.30 **PAUSE** 9.30-10.45 **Somatisk comorbiditet og medicingennemgang** 10.45-11.00 **PAUSE** 11.00-12.00 **Somatisk comorbiditet og medicingennemgang** 12.00-12.45 **FROKOST** 12.45-13.45 **Somatisk comorbiditet og medicingennemgang** 13.45-14.00 **PAUSE med kaffe** 14.00-15.00 **Case arbejde og diskussion**	Ann Lykkegaard Sørensen Overlæge Lars Peter Nielsen Overlæge Birgitte Klindt Poulsen
Modul 5	8.00-8.15 **Kaffe** 8.15-9.15 **Introduktion til deltagelse i "Effekt af kompetenceudvikling til psykiatriske sygeplejersker"** 9.15-9.30 **PAUSE** 9.30-10.45 **Introduktion til registrering af observationer og interventioner samt gennemgang af enkelte cases** 10.45-11.00 **PAUSE** 11.00 – 12.00 **Test af deltagernes viden** 12.00-12.45 **FROKOST** 12.45-13.45 **Fokusgruppeinterview** 13.45-14.00 **PAUSE** 14.00-15.00 **Afsluttende kommentarer fra deltagerne og farvel**	Ann Lykkegaard Sørensen, cand.scient.san og sygeplejerske

Appendix F. Registration form for nurses (Study III)

Study III.

Registreringsskema: Observationer vedrørende medicin

Sygeplejerskens ID (initialer):

Patientens CPR-nummer:

Patient ID:

Dato for medicinobservation:

1. Relevante blodprøver: *(udfyldes kun hvis observationerne relaterer sig hertil. F.eks forhøjet INR)*

Nyretal (e-GFR, crea):

Levertal (ALAT, INR):

S-Elektrolytter (Na, K):

2. Kategorier af PIP (potentially inappropriate prescribing)

Ved angivelse af PIP skal følgende kategorier anvendes:

0. *Ingen identificerede PIP*
1. *allergi*
2. *indikation (er der indikation for lægemidlet?)*
3. *dosis for lille*
4. *dosis for stor*
5. *interaktion mellem lægemiddel og sygdom*
6. *interaktion mellem lægemidler*
7. *dobbeltordination*
8. *uhensigtsmæssigt doseringsinterval*
9. *uhensigtsmæssig doseringstidspunkt*
10. *uhensigtsmæssig lægemiddelform*
11. *uhensigtsmæssig administrationsvej*
12. *uhensigtsmæssig behandlingsvarighed*
13. *POM(potential omission of medication) – indikation for et lægemiddel der **ikke** er ordineret*
14. *TDM (Therapeutic Drug Monitoring mangler)*
15. *Andet*

Registreringsskema: Observationer vedrørende medicin

Sygeplejerskens ID (initialer):

Patientens CPR-nummer:

Patient ID:

OBSERVATIONER

Nummer	Lægemiddelnavn(e)	ATC-kode(r)	Kategori af PIP	Beskrivelse af PIP
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Registreringsskema: Observationer vedrørende medicin

Sygeplejerskens ID (initialer):

Patientens CPR-nummer:

Patient ID:

OPFØLGNING/INTERVENTIONER (efter forelæggelse af observationer for læge)

2. Kategorier af konsekvenser/interventioner

Ved angivelse af konsekvenser/interventioner skal følgende kategorier anvendes :

0. *observation blev vurderet "klinisk ikke-relevant" og ingen intervention gennemførtes*
1. *observationen blev ikke vurderet og ingen intervention gennemførtes*
2. *observationen ledte til lægefaglig dokumentation i journalen (fx en manglende indikation, der angives i journalen) men ingen ændringer i ordinationer*
3. *observationen medvirkede eller ledte til et specialisttilsyn*
4. *observationen ledte til ordination af supplerende observation (fx blodprøver eller blodtryk)*
5. *observationen ledte til en ændring i 1 eller flere af følgende: doseringsinterval, doseringstidspunkt, lægemiddelform, administrationsvej, behandlingsvarighed*
6. *observationen ledte til seponering af 1 (eller flere lægemidler)*
7. *observationen ledte til dosisreduktion af 1 (eller flere lægemidler)*
8. *observationen ledte til dosisøgning af 1 (eller flere lægemidler)*
9. *observationen ledte til ordination af et nyt lægemiddel*
10. *observationen ledte til ordination af TDM (therapeutic drug monitoring)*
11. *Andet (VIGTIGT: før denne kategori vælges, bedes du kontrollere at din observation ikke kan placeres i én af ovenstående kategorier)*

Registreringsskema: Observationer vedrørende medicin

Sygeplejerskens ID (initialer):

Patientens CPR-nummer:

Patient ID:

Dato for lægefaglig stillingtagen:

OPFØLGNING (*bemærk at én observation muligvis leder til flere opfølgningskategorier)*

Nummer	Opfølgningskategori	Eventuel kort beskrivelse/kommentar
Ad 1		
Ad 2		
Ad 3		
Ad 4		
Ad 5		
Ad 6		
Ad 7		
Ad 8		
Ad 9		
Ad 10		

Appendix G. COnsolidated criteria for REporting Qualitative research (COREQ) (Study IV)

Study IV.

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	3
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	4
Occupation	3	What was their occupation at the time of the study?	4
Gender	4	Was the researcher male or female?	N/A
Experience and training	5	What experience or training did the researcher have?	4
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	3
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	3
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	3
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	4
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	2
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	3
Sample size	12	How many participants were in the study?	3
Non-participation	13	How many people refused to participate or dropped out? Reasons?	3
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	3
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	3
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	3
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	3+4
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	N/A
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	4
Field notes	20	Were field notes made during and/or after the inter view or focus group?	4
Duration	21	What was the duration of the inter views or focus group?	3
Data saturation	22	Was data saturation discussed?	14
Transcripts returned	23	Were transcripts returned to participants for comment and/or	N/A

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	4
Description of the coding tree	25	Did authors provide a description of the coding tree?	N/A
Derivation of themes	26	Were themes identified in advance or derived from the data?	4
Software	27	What software, if applicable, was used to manage the data?	4
Participant checking	28	Did participants provide feedback on the findings?	N/A
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	5-12
Data and findings consistent	30	Was there consistency between the data presented and the findings?	
Clarity of major themes	31	Were major themes clearly presented in the findings?	4-5
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	4-5

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

PAPERS

PAPER I. THE MEDICATION PROCESS IN A PSYCHIATRIC HOSPITAL: ARE ERRORS A POTENTIAL TREAT TO PATIENT SAFETY

Risk Management and Healthcare Policy

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open access to scientific and medical research

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ORIGINAL RESEARCH

The medication process in a psychiatric hospital: are errors a potential threat to patient safety?

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Purpose: To investigate the frequency, type, and potential severity of errors in several stages of the medication process in an inpatient psychiatric setting.

Methods: A cross-sectional study using three methods for detecting errors: (1) direct observation; (2) unannounced control visits in the wards collecting dispensed drugs; and (3) chart reviews. All errors, except errors in discharge summaries, were assessed for potential consequences by two clinical pharmacologists.

Setting: Three psychiatric wards with adult patients at Aalborg University Hospital, Denmark, from January 2010–April 2010.

The observational unit: The individual handling of medication (prescribing, dispensing, and administering).

Results: In total, 189 errors were detected in 1,082 opportunities for error (17%) of which 84/998 (8%) were assessed as potentially harmful. The frequency of errors was: prescribing, 10/189 (5%); dispensing, 18/189 (10%); administration, 142/189 (75%); and discharge summaries, 19/189 (10%). The most common errors were omission of pro re nata dosing regime in computerized physician order entry, omission of dose, lack of identity control, and omission of drug.

Conclusion: Errors throughout the medication process are common in psychiatric wards to an extent which resembles error rates in somatic care. Despite a substantial proportion of errors with potential to harm patients, very few errors were considered potentially fatal. Medical staff needs greater awareness of medication safety and guidelines related to the medication process. Many errors in this study might potentially be prevented by nursing staff when handling medication and observing patients for effect and side effects of medication. The nurses' role in psychiatric medication safety should be further explored as nurses appear to be in the unique position to intercept errors before they reach the patient.

Keywords: medication safety, mental health disorders, medication errors, psychiatry

Introduction

Adverse drug events (ADEs) and medication errors (MEs) are recognized as an important quality and patient safety problem in modern hospital settings, causing harm as well as avoidable morbidity and mortality.[1–5]

There is limited evidence about these issues in psychiatric settings. Only a few studies on ADEs and MEs in psychiatric hospital settings exist. Four of these studies addressed prescribing errors and two studies addressed administration errors.[6–11]

Results from three of the studies investigating prescribing errors displayed a rate of decision-making errors which ranged from 12.5%–23.7% and a rate of documentation (clerical) errors, which ranged from 76.3%–84.5%.[7–9] The fourth study, aimed at describing errors in the prescribing phase, was based on reports

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http://dx.doi.org/10.2147/RMHP.S47723

about pharmacists' interventions.[6] In the two studies which focused on administration errors, one study was based on self-reporting by nurses and did not report any rate of error. The other study was an observational study of administration errors in elderly psychiatric inpatients where administration errors were detected in 25.9% of all opportunities for error.[10,11] Some studies have investigated several stages in the medication process, but these studies were primarily based on data collected from self-reporting of medication errors and chart reviews.[12–15] These studies measured their outcomes using different methods and denominators which makes it difficult to conduct comparisons. However, it is recognized that direct observation is the most valid method when collecting data in the dispensing stage and the administration stage.[16] It is highly important to apply reliable methods when investigating frequency and character of errors in the medication process to produce valid and precise information.[16,17]

To our knowledge, there are no studies in psychiatric hospital settings which focus on errors in more stages of the medication process, including discharge summaries, by applying the most sensitive methods of detection. A precise estimate of frequency, type, and potential severity of errors is needed to choose relevant interventions to reduce errors in the medication process. Therefore, the objective of this study was to investigate the frequency, type, and potential severity of errors in several stages of the medication process in an inpatient psychiatric setting.

Materials and methods

The medication process can be divided into prescribing, dispensing, administering, and monitoring.[18]

Furthermore, the prescription stage of the medication process can be divided into a decision-making process and a clerical process. The decision-making process concerns the physician's choice of drug, dose, and form of administration.[18] The stage of monitoring the patient for effects and side effects was not included in the study.

An error was defined as "a planned action which failed to achieve the desired consequences."[19] This means that all deviations from guidelines were considered errors; subsequently, two clinical pharmacologists evaluated all errors for potential severity, thereby separating harmless errors from errors with the potential to harm patients.

Describing proportions of errors requires a defined denominator.[20]

"Opportunities for error", defined as opportunities for active errors (omissions, mistakes, and/or conscious or unconscious rule violations), was the denominator used to calculate the proportion of errors in this study. The denominator is established by multiplying the number of handled medications with the number of requirements in the guidelines to be followed. The proportion of errors was the sum of actual errors divided by the total number of opportunities for errors.

Design

The study was designed as a descriptive, cross-sectional study of errors in the medication process and potential harm. Data was collected using three methods: direct observation; unannounced visits to the wards to collect dispensed drugs for identification; and chart review. The study population included in-hospital patients aged 18 or above (n = 67), nurses and nurses' assistants dispensing and administering drugs, and physicians prescribing drugs, but the observational unit was the individual handling of medication (prescribing, dispensing, and administering). It is common in Denmark that each ward has its own stock ward system where nurses dispense drugs. The term "dispensing" refers to nurses identifying the drugs prescribed and dispensing it to medication cups. Subsequently, the nurses will administer the medications to patients. The hospital pharmacy staff undertakes monitoring the use, needs, and reordering of drugs as well as giving advice for the individual wards. In this study, regular and pro re nata (PRN) prescriptions were included, apart from discharge summaries in which PRN prescriptions were excluded. The choice of excluding PRN prescriptions in discharge summaries was made because physicians often forget or are not aware that a PRN drug deliberately not prescribed in the discharge summary must be discontinued in the computerized physician order entry (CPOE). Including this as an error type would give a distorted impression of the prevalence of errors in discharge summaries. PRN prescriptions are prescriptions not scheduled to be administered at predetermined times of the day but to be used "when needed." Errors in discharge summaries were not evaluated for potential severity, due to practical reasons. Included drug forms were tablets, capsules, mixture, suppositories, and injections.

Study site

This study was conducted in three psychiatric wards at Aalborg University Hospital, Denmark, from January 2010 to April 2010. Physicians were responsible for prescribing drugs and nurses or nurses' assistants were responsible for dispensing and administering medication. There was no

administration of drugs scheduled in the night shift. Drug prescriptions were documented in a CPOE system.

Methods for collecting data

All comparisons of observations to the CPOE were conducted by one of the authors (ALS).

Observational method

Data were collected on the wards using direct observation. The observer spent two day shifts (8 hours) and one evening shift (8 hours) on each ward, observing the nurse or nursing assistant responsible for dispensing and administering drugs. The observations covered six rounds of dispensing and administering drugs in each of the three wards. The caregiver responsible for the entire medication administration in the ward was aware of the study purpose but had no knowledge about which actions were observed and registered. The observations of dispensed and administered drugs were registered on a structured paper form and subsequently compared with prescriptions in the CPOE. Due to the tradition and rules of observing the patients' consumption of medication in psychiatric nursing, it was possible to register all administered medication. Any discrepancies between the observed and the prescribed medication in the CPOE were classified as errors, according to the criteria outlined in Table S1.

Unannounced visit to the ward

The unannounced visit to the ward was conducted approximately 3 weeks after the observational study. The dispensed medication was collected from the medication storage room before administration. The medicine collected from the medication storage room was subsequently compared to the CPOE. Any discrepancies between the identified drugs and the prescriptions in the CPOE were classified as errors, according to the criteria outlined in Table S1.

Chart review

The CPOE and discharge summaries were retrospectively screened for errors. It was assessed whether drug prescriptions were in accordance with the criteria outlined in Table S1. If a patient was sampled more than once, only new or altered prescriptions were screened for errors. Discharge summaries were also screened to identify errors, ie, discrepancies between eligible prescriptions in the CPOE and the discharge summaries, according to the criteria outlined in Table S1.

Potential clinical consequences

All registered errors in the observational study, screening of the CPOE (errors in discharge summaries excluded), and the unannounced visits to the wards to collect dispensed drugs were assessed for potential clinical consequences. The assessment was conducted independently by two senior clinical pharmacologists using a four-scale system: potentially fatal; potentially serious; potentially significant; and potentially nonsignificant.[5] The four-scale classification system can be found in Table S2.

Statistics

All data were analyzed using Stata/IC 10.0 (StataCorp, College Station, TX, USA). Frequencies were described as percentages. The kappa test was used to evaluate the inter-rater variation in the clinical pharmacologists' assessment of potential clinical consequences where appropriate. The statistical significance level was set at 0.05.

Ethics

Approval of the study was obtained from the Danish Data Protection Agency. The investigator was ethically obliged to intervene in the case of observing an error. If the investigator had to intervene, it was registered as an error.

Results

Patients

The study included 67 eligible patients (24 men [36%] and 43 women [64%]) with a mean age of 46 years (20–79 years). The most common reason for admission was schizophrenia and other psychotic disorders (22/67;33%), followed by bipolar disorders (11/67;16%).

Frequency of errors

A total of 189 errors were detected in 1,082 (17%) opportunities for errors. The frequency of errors in the different stages of the medication process is shown in Table 1. The majority of errors were detected in the administration stage with errors in 142/340 (42%) opportunities for error. This was followed by discharge summaries with errors in 19/84 (23%) opportunities for error. Nine (47%) errors in discharge summaries were due to eligible prescriptions in the CPOE, which were not prescribed in the discharge summary.

The intention behind investigating the dispensing stage using two methods was to examine the validity of the results obtained in the observational study. There were errors in 9/324 (3%) opportunities for error of the dispensed drugs in

Table 1 Frequency of errors in the different stages of the medication process

Prescribing, CPOE n/N_{total} (%)	Dispensing, observational study n/N_{total} (%)	Dispensing, unannounced visit n/N_{total} (%)	Administration n/N_{total} (%)	Discharge summaries n/N_{total} (%)
10/267 (4)	9/324 (3)	9/67 (13)	142/340 (42)	19/84 (23)

Notes: N_{total}, the total number of opportunities of errors in each stage (prescription and doses); n, the total number of detected errors in each stage of the medication process. The difference in number of dispensed medications and number of administered medications in the observational study was due to incidents where staff had administered medicine without the investigators' presence.
Abbreviation: CPOE, computerized physician order entry.

the observational study and in (9/67) 13% of the dispensed drugs in the unannounced control visit of which the majority was associated with one nurse assistant. Fewest errors were detected in the prescribing stage.

Frequency of error types

The identified errors were distributed by error types which are shown in Table 2. The most frequent error types were lack of identity control (135/142; 95%) and concordance with drug prescription (10/142; 7%). The error type lack of identity control occurs when the patients' identity is not established before administering drugs. The clinical guideline states that the person administering the drugs must identify the patient by having the patient say his full name and Social Security number, or by using the obligatory wristband to identify the patient. The error type concordance with drug prescription occurs if already-dispensed drugs are delegated to another staff member; this person must compare the drugs to be administered with the prescriptions in the CPOE. Error types in the administration stage could be mutually dependent. This occurred with the following error types: "lack of identity control;" "wrong time;" and "lack of correct labeling." The dependency arises because each of the aforementioned error types affects all doses which were delivered to the patient in that particular incidence. Analysis of these error types showed that "lack of identity control" occurred in 49 of 137 (36%) deliveries. "Wrong time" occurred in four of 137 (3%) deliveries. Finally, "Lack of correct labeling" occurred in three of 137 (3%) deliveries.

Assessment of potential clinical consequences

The assessment of the potential clinical consequences was carried out in a worse-case scenario, meaning that whenever the clinical pharmacologists disagreed on the severity of an error, the most severe assessment was included in the analysis. Results from the assessment are displayed in Table 3; definitions are outlined in Table S2. The inter-rater agreement (measured by the test statistic kappa) for errors in prescribing, dispensing, and administration varied from good to perfect (0.54; 0.75; 0.82; and 1.0, respectively).[21]

The pharmacologists assessed 84/998 (8%) errors as potentially serious or potentially fatal. The number of opportunities for error in this part of the study was reduced to 998 because assessment of potential clinical consequences did not include errors in discharge summaries. The four potentially fatal errors were related to the error types: "omission of PRN dosing regime" (n = 2) and "lack of identity control" (n = 2). There were errors in 142/340 (42%) of all opportunities for errors in the administration stage, and it was assessed that 75/142 (53%) of these errors had the potential to harm patients.

Drug categories and errors

Errors with the potential to harm patients were most often associated with drugs related to the patients' psychiatric condition (Table 4). The drug category most often associated with these errors was psycholeptics. The type of drug most often involved in potential harmful errors was atypical antipsychotics, followed by anxiolytic-sedative drugs and mood stabilizers. The errors assessed to be potentially fatal were related to prescribing and administration of medication and were associated with analgesics (opioids) (n = 2) and psycholeptics (atypical antipsychotics) (n = 2). Nonpsychiatric drugs associated with potential harmful errors constituted 7/77 (9%). The majority of these errors were anti-inflammatory and antirheumatic drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs).

Discussion

There were errors in almost one-fifth of all handlings of medication of which the vast majority occurred in the administration stage. The main type of errors was lack of identity control. The prevalence of potentially harmful errors was 8%, of which 0.3% errors were considered potentially fatal. The potentially fatal errors involved drugs from the categories of analgesics and psycholeptics. A few other studies in psychiatry have examined administration errors and identified

Table 2 Frequency of error types in the different stages of the medication process

Stage in medication process	Total number of doses or prescriptions affected with at least one error in each stage of the medication process (N)	[a]Total number of error types in each stage (n/N)
Prescribing, CPOE	N = 10	
Drug name		0
[b]Drug prescription		2/10
[c]Omission of PRN dosing in CPOE		8/10
Dispensing, observational study	N = 9	
Drug prescription		0
Omission of dose		3/9
Wrong dose		1/9
Unordered dose		0
Contamination		1/9
Lack of correct labeling		4/9
Dispensing, unannounced control visit	N = 9	
Drug prescription		0
Omission of dose		6/9
Wrong dose		2/9
Unordered dose		1/9
Administration	N = 142	
Omission of dose		0
Wrong dose		1/142
Unordered dose		0
Contamination		0
[d]Lack of correct labeling		0
[e]Wrong time		8/142
Wrong route		0
Wrong administration technique		0
[f]Lack of identity control		135/142
Wrong patient		0
[g]Concordance with drug prescription		10/142
Discharge summaries	N = 19	
Drug name		1/19
Drug prescription		9/19
Omission of drug		9/19

Notes: [a]One dose or prescription affected by an error could be associated with more than one error type; [b]drug prescription: means one or more errors (including omissions) in strength per unit, route of administration, form of administration, dose, frequency of administration, signature, date, duration of treatment (only antibiotics was included in this study); [c]omission of PRN dosing regime in CPOE: means one or more errors (including omissions) in strength per unit, route of administration, form of administration, dose, frequency of administration, signature, date, duration of treatment; [d]lack of correct labeling: means that all drugs administered to patients must be marked with the patient's full identity; [e]wrong time: means the drugs were administered ±60 minutes off the scheduled time; [f]lack of identity control: means that the patient's identity has not been established by having the patient state full name and Social Security number or using the obligatory wristband; [g]concordance with drug prescription: means that when dispensed drugs are delegated to another staff member, this person must compare the drugs to be administered with the prescriptions in the CPOE.
Abbreviations: CPOE, computerized physician order entry; PRN, pro re nata.

the error types mismatching between medication and patient and wrong patient. One study found mismatching between medication and patient to occur with the second highest frequency; whereas, the second study found wrong patient to constitute 4/108 (3.7%) of all administration errors.[10,14] These results emphasize the importance of systematically identifying patients to secure the right medication for the right patient. We found that administration errors constituted 142/340 (42%) of all errors, which is in contrast to a USA study of several stages in the medication process, which demonstrated that 10% of all medication errors were identified in the administration stage.[15] This disparity is most likely due to variation in error types. In an observational study of administration errors in elderly psychiatric patients, errors were identified in 369/1423 (25.9%) of opportunities for error. However, this result is not entirely comparable, because the aforementioned study did not include the error type lack of identity control or any of the related error types, such as wrong patient or mismatching between medication and patient.

The severity of administration errors in psychiatric settings has been assessed less severe when compared

Table 3 Categories of potential clinical consequences of errors in the medication process

	Nonsignificant n (%)	Significant n (%)	Serious n (%)	Fatal n (%)	Interrater variation
Prescribing, CPOE	0	4 (40)	4 (40)	2 (20)	$\kappa = 1,0^a$
Dispensing, observational study, n (%)	0	6 (66)	3 (33)	0	$\kappa = 0.82^a$
Dispensing, unannounced visit, n (%)	4 (44)	5 (56)	0	0	$\kappa = 0.75^a$
Administration, n (%)	29 (20)	38 (27)	73 (51)	2 (1)	$\kappa = 0.54^a$

Notes: [a]Kappa test for interrater agreement; the highlighted areas represent errors with the potential to harm patients.
Abbreviation: CPOE, computerized physician order entry.

to administration errors in somatic hospital settings.[11,15] However, this study assessed more than one-half of all administration errors to be potentially serious. Many hospitals have introduced wristbands as a means to control patients' identity, including the psychiatric hospital where our study was carried out. In a study of how and whether nurses identify patients in a psychiatric hospital setting, it was found that the use of wristbands was erratic and influenced by a psychiatric nursing culture rooted in the belief that (good) nurses know who the patients are.[22] The inconsistency in using the patient's wristband for identification has also been addressed in somatic settings, and it has been shown in simulation tests that as many as 61% of nurses do not discover an unexpected identity error.[23,24] This raises a question about how and when nursing culture plays a role in patient safety and whether this brings advantages or barriers. Nurses are involved in many errors, but nurses also prevent many errors from happening.[25] It needs to be considered that nurses are the professionals spending most time with the patients and, therefore, function as gatekeepers, where they can prevent errors and harm from reaching the patient. Nurses are coordinating several aspects of care to patients, including the care delivered by other health care professionals, and this is a major contribution to patient safety.[26]

Errors in discharge summaries constituted 10% (19/189) of all errors detected in the study. It is not possible to compare these results directly to other studies due to definitions and categorizations; however, earlier studies of errors in discharge summaries in general hospital settings have found discrepancies in 2%–76% of the prescribed drugs.[5,27,28]

It has been asserted that surgery and psychiatry are associated with the highest rate of dispensing errors and, therefore, it appears reasonable to consider psychiatry a high-risk specialty, in regards to dispensing errors.[29] We investigated dispensing errors using observation and unannounced control visit, which showed a difference in results. When using observation and unannounced control visit to identify dispensing errors the rate of errors was 9/324 (3%)

Table 4 Categories of drugs involved in errors with potential to harm patients

Drug category	Prescribing	[a]Dispensing (observational and unannounced control visit)	Administration
N Nervous system			
N02 Analgesics	2	0	0
N03 Antiepileptics	0	0	9
N05 Psycholeptics			
– Atypical antipsychotics	3	3	20
– Typical antipsychotics	0	1	9
– Anxiolytic-sedative	1	0	17
– Other	0	0	3
N06 Psychoanaleptics			
– Mood stabilizers	0	0	9
N07 Other nervous system drug	0		1
M Musculoskeletal system			
M01 Anti-inflammatory and antirheumatic products			6
H Systemic hormonal preparations, excluding sex hormones and insulins			
H03 Thyroid therapy			1

Notes: Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) Classification System (World Health Organization Collaborating Centre for Drugs Statistics Methodology [WHOCC]). [a]In this table, the observational and unannounced control visit in the dispensing stage have been collapsed.

and 9/67 (13%), respectively. The difference in identified errors is caused by dependency in data, which arises due to the few nurses and nurses' assistants involved in dispensing and administering medication. When pooling the results from the dispensing stage, the error rate was 18/391 (5%). This result is supported by other studies not depending on unit dose systems which found error rates <1% and up to 5%.[5,29,30] The most common error type in the dispensing stage was omitted dose, which is in accordance with a previous study using similar methods of error detecting but in a general hospital setting.[5]

In this present study, the clinical pharmacologists assessed three errors in the dispensing stage to be potentially serious, and no errors were assessed as potentially fatal. To our knowledge, there are no other studies in psychiatry where observed dispensing errors have been assessed for severity.

There were few prescription errors, but the prescription stage represented one-half of the potential fatal errors. Most of the prescribing errors were of the type "lack of PRN regime," which is a type of prescription error that nurses are capable of intercepting. On the other hand, it also places nurses in a situation where they possibly make independent decisions as to whether a PRN medication is appropriate. The use of PRN medication is often solely the nurses' decision and, perhaps, due to a lack of research into the use of PRN medication as an intervention in mental health care, the practice varies considerably.[31]

Strengths and weaknesses in the study

The majority of studies on medication errors and psychopharmacotherapy have been conducted in general hospital settings, and very few studies include a psychiatric population. Thus, this study is an important contribution to the current knowledge, as it focuses on errors in several stages of the medication process by applying the most sensitive method to each stage in a psychiatric hospital setting. There were 67 patients included in the study, which is a relatively small sample and a potential weakness in the study. Observation as a method of detecting errors is considered a valid and well-tested method; in this study, we sought to substantiate the validity of observing for errors with the unannounced control visit.[17,32] The difference in errors identified by observation and the unannounced control visit is solely due to the dependency in data caused by the few nurses and nurses' assistants participating in the study. In this study, dispensing of drugs was done by nurses and nurses' assistants, which might complicate comparisons with other hospitals and settings where hospital pharmacies undertake the dispensing of drugs. It appears the study has a good internal validity, but the study was carried out in a single university hospital, thus producing a limited external validity. However, it is evident that psychiatric university hospitals – in comparison with somatic hospitals – are equally challenged in improving the quality of the medication process.

Conclusion

Errors were found in almost one-fifth of all handlings of medication, and a proportion of these errors had the potential to harm patients. In this study, the majority of errors involved psycholeptics, but potential fatal errors also involved analgesics. Most errors were found in the administration stage, and studies suggest that both nursing culture as well as an irregular practice regarding the patient's identity wristband could be a risk factor for not checking the patient's identity. This could lead to the error type "wrong patient." It might be beneficial to address nursing culture as well as awareness of existing clinical guidelines. Further studies are needed to investigate how and whether nurses influence medication safety for in-hospital psychiatric patients and how nurses can improve the quality of medication and medication safety for psychiatric patients.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary tables

Table S1 Criteria and definitions for error types

Stage in medication process	Definition	Error types
Prescribing	Unambiguous prescription	Omission of drug name, drug formulation, route, dose, dosing regime, date, signature, length of treatment time where required
Dispensing	Dispensed medication is concordant with prescribed drug in electronic medication chart	Wrong drug, unordered dose, omission of dose, wrong dose, wrong drug formulation, contamination (ie, touching tablets without gloves), control of prescription (ie, controlling that only prescribed drugs are dispensed), ambiguous labeling of medication
Administering	The right medication to the right patient in the right way and at the right time	Wrong: dose, administration technique, route, time (±60 minutes), unordered drug, unordered dose, omission of dose, lack of identity control, wrong patient (one or more medications administered to the wrong patient), contamination, concordance with drug prescription
Discharge summaries	Eligible prescriptions in medical record are identical to prescriptions in discharge summaries	Discrepancy in: drug name, drug formulation, route, dose, regime, omission of drug, unordered drug

Note: Adapted with permission from Lisby M, Nielsen LP, Mainz J. Errors in the medication process: frequency, type, and potential clinical consequences. *Int J Qual Health Care*. 2005.
Abbreviation: CPOE, computerized physician order entry.

Table S2 Definition of potential clinical consequences

Category	Definition	Definition of keywords
Potentially fatal	Errors judged to imply a potential clinical risk for causing the death of the patient	Fatal refers to errors that could lead to the death of the patient
Potentially serious	Errors judged to imply a potential clinical risk of injuring the patient	Injury includes errors that would require active treatment to restore the health of the patient. A potentially serious error would lead to either permanent or temporary disability
Potentially significant	Errors judged to imply a potential clinical risk of being "inconvenient" for the patient – without causing any harm or injury	"Inconvenient" refers to unpleasant consequences of wrong dose/drug omission of dose/drug that could lead to pain, dizziness. It also refers to any monitoring of the patient, such as extra blood test, measurement of blood pressure
Potentially nonsignificant	Errors judged to be without any potential clinical risk for the patient	Without clinical risk refers to errors that did not lead to any injury or inconvenience for the patient

Notes: The highlighted areas represent errors with the potential to harm patients. Adapted with permission from Lisby M, Nielsen LP, Mainz J. Errors in the medication process: frequency, type, and potential clinical consequences. *Int J Qual Health Care*. 2005.

Reference

1. Lisby M, Nielsen LP, Mainz J. Errors in the medication process: frequency, type, and potential clinical consequences. *Int J Qual Health Care*. 2005;17(1):15–22.

PAPER II. POTENTIALLY INAPPROPRIATE PRESCRIPTIONS IN PATIENTS ADMITTED TO A PSYCHIATRIC HOSPITAL

NORDIC JOURNAL OF PSYCHIATRY, 2016
VOL. 70, NO. 5, 365–373
http://dx.doi.org/10.3109/08039488.2015.1127996

Taylor & Francis
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RESEARCH ARTICLE

Potentially inappropriate prescriptions in patients admitted to a psychiatric hospital

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ABSTRACT

Background Very little is known about the general appropriateness of prescribing for psychiatric patients. **Aims** To identify prevalence and types of potentially inappropriate prescribing (PIP) of psychotropic and somatic medications, to assess the severity of potential clinical consequences and to identify possible predictive factors of PIP in a sample of adult psychiatric in-patients. **Methods** A descriptive, cross-sectional design using medication reviews by clinical pharmacologists to identify PIP during a 3-month period. The setting was in-patient units in a psychiatric department of a Danish university hospital during a 3-month period (September 2013–November 2013). Patients medication lists (n = 207) were reviewed at the time of admission and all identified PIPs were assessed for potential consequences by clinical pharmacologists. **Results** There were 349 PIP identified in 1291 prescriptions. The proportion of patients found to have at least one PIP was 123/207 (59%) and the proportions of patients with at least one PIP assessed to be potentially serious or fatal was 69/207 (33%) and 24/207 (12%), respectively. Interactions between drugs 125/207 (36%) and too high doses of drugs 56/207 (16%) were the most frequent PIP. Predictive factors for PIP were polypharmacy (>5 prescriptions) and having one or more somatic diagnoses. **Conclusion** PIP is common in psychiatric patients and potentially fatal. Particularly polypharmacy (>5 prescriptions) and concomitant somatic illness were associated with the probability of PIP. Improving the quality of prescribing might benefit from an interprofessional approach and thus better training of physicians and nurses is needed in order to minimize PIP.

ARTICLE HISTORY
Received 19 June 2015
Revised 2 November 2015
Accepted 29 November 2015
Published online 28 January 2016

KEYWORD
Clinical pharmacologists; medication review; medication safety; potentially inappropriate prescribing

Medication errors (MEs) happen frequently in hospital settings and they have been acknowledged as a major problem across health care systems (1–4). Studies have unanimously shown that in the wake of MEs, increased mortality, morbidity and increased costs for society, hospitals and patients follow (1,5–8). For several years, psychiatry received little attention in the context of patient safety but in 2006 the Institute of Medicine report *Preventing Medication Errors* concluded that MEs needed further study in mental health settings (9). Following the report, it has been demonstrated that prescribing errors in psychiatry are a frequent problem and may potentially harm patients (10–16). The terminology used in this study is shown in Table 1 (1,17–21).

Prescribing drugs for adult psychiatric patients is a highly complex task due to the nature of psychiatric conditions and somatic co-morbidity (22,23). Consequently, balanced prescribing (19) might be difficult to achieve and prescribing may become less appropriate. Balanced prescribing encompasses considerations on drugs prescribed for both psychiatric and somatic illnesses. This crossfield has rarely been touched upon in the literature but a French study on inappropriate prescribing for elderly patients with cognitive or psychiatric co-morbidity concluded that risk factors for inappropriate prescriptions amongst others were number of concomitant prescriptions and being cognitively impaired. Additionally, it was concluded that risk factors for omission of prescriptions (under-use) were psychiatric disorders and increased level of somatic illness (24). The uncertainty of causality and the complexity physicians face when prescribing drugs for psychiatric patients increases the risk of potentially inappropriate prescribing (PIP). ''Potentially inappropriate prescribing'' is a term that also reflects the subjectivity related to the issue, e.g. ''appropriateness'' depends on the quality and relevance of the evidence, viewpoints of the clinician and patient, and the patient's circumstances and treatment goals (25). Nonetheless, in order to develop realistic, preventive strategies there is a need to establish the prevalence, type and severity of PIP in mental health settings. Given the complexity of evaluating the

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Supplemental data for this article can be accessed here.

Table 1. Terminology and definitions.

Terminology	Definition
Medication error (ME)	An error in the stages of the medication process – ordering, dispensing, administering, and monitoring the effect – causing harm or implying a risk of harming the patient (17)
Adverse drug events (ADEs)	Any injury resulting from medication use, including physical harm, mental harm, or loss of function (1)
Adverse reaction (AR)	An adverse reaction is a response to a medicinal product which is noxious and unintended; this includes adverse reactions which arise from • Use of a medicinal product within the terms of the marketing authorization • Use outside the marketing authorization including overdose, misuse, abuse and medication errors • Occupational exposure (18)
Balanced prescribing	A process that recommends a medicine appropriate to the patient's condition and, within the limits created by the uncertainty that attends therapeutic decisions, a dosage regimen that optimizes the balance of benefit to harm (19)
Potentially inappropriate prescribing (PIP)	Prescribing that introduces a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for the same condition. Additionally, PIP includes the use of drug combinations with known drug–drug interactions, drug–disease interactions, over-dosing, use of drugs for longer time than clinically indicated, as well as lack of prescribing drugs that are clinically indicated (20,21)
Pro re nata (PRN)	A prescribed medication which is not scheduled but administered as needed.

possible clinical outcome for psychiatric patients, medication reviews performed by clinical pharmacologists with in-depth knowledge of psychiatry and somatic illness would presumably serve as the best available "golden standard". Studies on medication safety in psychiatry have so far focused on medication errors and not the general appropriateness of prescribing, including the under-use of drugs. Therefore the aims of this study were to identify prevalence and types of PIP, to assess the severity of potential clinical consequences and to identify possible predictive factors of PIP in a sample of adult psychiatric in-patients.

Materials and methods

Study design and setting

This study was designed as a descriptive, cross-sectional study using medication reviews by clinical pharmacologists to identify PIP in a psychiatric population. The study was carried out in the Department of Psychiatry of Aalborg University Hospital, Denmark, which provides mental health services for the entire Northern Denmark region (approximately 580 000 individuals). Mental health care for adult psychiatric inpatients in the Northern Denmark region is organized in 14 specialized units aimed at acute psychiatry, bipolar disease and depression, psychotic illnesses and personality and anxiety disorders. Each year the psychiatric university hospital receives approximately 2800 adult patients and when patients are admitted to the psychiatric emergency ward, approximately 70% of the patients are discharged within 24–72 h.

Study population

This study included data from 226 consecutive patients. The inclusion criterion was admission due to any psychiatric condition during a 3-month period (1 September to 31 November 2013) to one of the 14 different units. Patients with end-stage terminal illness, dual admissions to somatic hospitals, non-obtainable medical records or no prescriptions were excluded. The patients were admitted by their general practitioner or via the psychiatric emergency ward. Forensic and child/adolescent patients were not included in the study.

Data collection

There is no universally accepted definition of medication review but it has been described as a systematic assessment of the pharmacotherapy of an individual patient that aims to evaluate and optimize patient medication by a change (or not) in prescription, either by a recommendation or via a direct change (26). The medication reviews in this study followed a 3-step procedure illustrated in Figure 1, which is a procedure adapted from a Danish PhD thesis implementing medication reviews by clinical pharmacologists (27).

Patient interview and documented recommendations to the ward physician are included in the original procedure (26) but were omitted in this present study (except for findings of utmost urgency). Patient interviews as an addition to usual care were left out because it was assessed that patients would be needlessly burdened in an already vulnerable situation. Reporting to the hospital physician was left out due to the study's descriptive rather than interventional design. All identified PIPs were categorized according to types of decision errors in the prescribing stage of the medication process (17). Categories and descriptions of PIPs are listed in Table 2.

The clinical pharmacologists also assessed the potential severity of each PIP using a 4-point scale (potentially non-significant, potentially significant, potentially serious and potentially fatal) which was applied in a previous study of errors in the medication process (13). The 4-point scale is reproduced in Table 3.

Ethics

The study was approved by the Danish Health and Medicines Authority, The Danish Data Protection Agency and the hospital management, but did not require permission from the Regional Scientific Ethics Committee. According to national legislation, patient consent was not obtained because the study was an internal audit of the quality of treatment in the psychiatric hospital. The clinical pharmacologists were ethically obliged to intervene if the medication review called for immediate response. A clinical pharmacologist contacted a ward on two occasions and the patients' medications were reviewed and altered in collaboration with a ward physician.

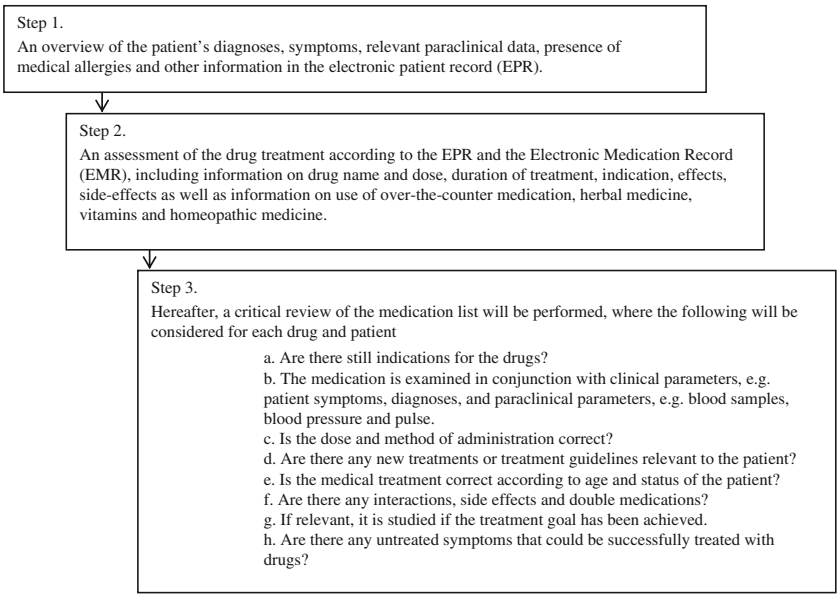

Figure 1. The process of medication review by clinical pharmacologists. Adapted from Bonnerup (27).

Table 2. Categories and descriptions of potentially inappropriate prescribing (PIP).

Categories of potentially inappropriate prescriptions (PIP)	Description
Allergy	The patient develops an adverse reaction (AR)(18) caused by an abnormal immune response to a medication
Omission of indication for treatment	There is inadequate documentation in the EMR of the indication for treatment
Drug dosage too low	The dose is too low to achieve the goal of therapy and/or below the recommended minimum dose in the EPAR for the drug (http://www.ema.europa.eu/ema/). If the drug is not evaluated by the EMA then the product resume supplied by the Danish Medicines and Health Authority (https://sundhedsstyrelsen.dk/da/medicin/find-medicin/produktresumeer) has been applied
Drug dosage too high	The dose is above the recommended maximum dose in the EPAR for the drug (http://www.ema.europa.eu/ema/). If the drug is not evaluated by the EMA then the product resume supplied by the Danish Medicines and Health Authority (https://sundhedsstyrelsen.dk/da/medicin/find-medicin/produktresumeer) has been applied
Interaction between drugs	The pharmacological result of two or more drugs interacting both pharmacokinetically and pharmacodynamically
Interaction between drug and disease	The drug has the potential to interact with the patient's underlying illness(es) and cause harm to the patient
Duplicate drug	The duplicate prescribing of the same medication product or the same therapeutic medication class
Inappropriate dosing interval	The time intervals between doses are too short or too long to achieve an appropriate clinical outcome
Inappropriate dosing time	The drug has been prescribed for an inappropriate time of day
Inappropriate route of administration	The drug has been prescribed to be administered via another route than the first choice according to guidelines and without documentation for the relevance of the route of administration
Inappropriate duration of treatment	The duration of therapy is inappropriate according to guidelines
Omission of a potentially useful medication	The patient is eligible for drug therapy to treat an existing medical condition or reduce the risk of developing a medical condition. This assessment should be based on current guidelines
Other	E.g. omission of relevant therapeutic drug monitoring or ECGs

EMA: European Medicines Agency; EMR: electronic medication record; EPAR: European Public Assessment Report.

Results

Patients

There were 226 patients admitted during the study period (1 September to 31 November 2013) and 19 patients were excluded. Of the 19 patients excluded two were terminally ill, three had a ''dual'' admission to a somatic hospital where they were hospitalized, for two patients it was not possible to gain access to the patients' medical records, and the remaining twelve patients were not prescribed any drugs and were thus not eligible, resulting in 207 patients (Figure 1). The demographic data for the patients are displayed in Table 4.

It was found that 71/207(33%) of the patients had one or more somatic diagnoses. The 207 patients included in the study represented 1291 prescriptions distributed in 900 regular prescriptions and 391 PRN prescriptions, respectively.

Table 3. Definition of potential clinical consequences.

Category	Definition	Definition of keywords
Potentially fatal	**Errors judged to imply a potential clinical risk for causing the death of the patient**	**"Fatal" refers to errors that could lead to the death of the patient**
Potentially serious	**Errors judged to imply a potential clinical risk of injuring the patient**	**"Injury" includes errors that would require active treatment to restore the health of the patient. A potentially serious error would lead to either permanent or temporary disability**
Potentially significant	Errors judged to imply a potential clinical risk of being inconvenient for the patient – without causing any harm or injury	"Inconvenient" refers to unpleasant consequences of wrong dose/drug omission of dose/drug that could lead to pain, dizziness. It also refers to any monitoring of the patient such as extra blood tests, measurements of blood pressure
Potentially non-significant	Errors judged to be without any potential clinical risk for the patient	"Without clinical risk" refers to errors that would not lead to any injury or inconvenience for the patient

Bold type represents errors with the potential to harm patients.
Reproduced from Lisby M, Nielsen LP, Mainz J. Errors in the medication process: frequency, type, and potential clinical consequences. *Int J Qual Health Care*. 2005, by permission of Oxford University Press.

Table 4. Characteristics of the study population (N = 207).

Gender	N	%
Male	95	46
Female	112	54
Age (mean (range))	42 (18–83)	
Primary psychiatric conditions (ICD-10)		
Schizophrenia and other psychotic disorders	77	37
Affective disorders	68	33
Other[a]	62	30
Somatic morbidities		
Cardiac disease[b]	21	10
Diabetes mellitus 2	17	8
COPD	14	7
Patients with alcohol and/or substance abuse	71	33

COPD: chronic obstructive pulmonary disorder; ICD-10: *International Statistical Classification of Diseases and Related Health Problems*, tenth edition.
[a]Other examples include patients without diagnosis at the time, organic disorders and developmental disorders.
[b]Cardiac disease includes patients with coronary artery disease, arrhythmias, congestive heart failure and subsequent conditions thereof.

Potentially inappropriate prescribing

In total, 349 PIP were identified in 207 patients within 1–3 days after admission. The median number of regular prescriptions in the study population was four, but 26/207 patients (13%) had more than 10 regular prescriptions. The proportion of patients with at least one PIP was 123/207 (59%) and the proportions of patients with at least one PIP assessed to be potentially serious or potentially fatal were 69/207 (33%) and 24/207 (12%), respectively. Categories, frequency and severity of potential clinical consequences are displayed in Table 5.

The majority of potential problems in the category "Other" were related to identified potential ARs, e.g. sleep disturbances, but also problems such as lack of therapeutic drug monitoring and ECGs, or lack of response to test results that were out of range. In the category "Interaction between drug and disease," cardiac disease occurred most frequently 4/32, 13%) followed by chronic obstructive pulmonary disorder (3/32, 9%). In total, 45/349 (13%) of all PIP were assessed as potentially fatal. Of the 32 drug–drug interactions considered potentially fatal, 15/32 (47%) concerned two or more antipsychotic drugs and 12/32 (37%) drug–drug interactions concerned one or more antipsychotic drugs in combination with antidepressants. The remaining 5/32 (16%) drug–drug interactions considered potentially fatal involved the drugs propranolol, erythromycin and simvastatin. Finally, the category "Omission of a potentially useful medication" only constituted 16/349 (5%) of all PIP but all omissions referred to medications for somatic illness.

Characteristics and high-risk drugs associated with potential inappropriate prescribing

The logistic regression analyses of factors which may be predictors of PIP are presented in Table 6. Only polypharmacy (>5 prescriptions) and number of somatic diagnoses had a significant predictive value for PIP.

Subgroup analysis combining potentially severe and potentially fatal PIPs showed that polypharmacy (>5 prescriptions) produced a higher risk of potentially harming patients (RR = 2.42, 95% CI = 1.64–3.56) than compared to patients receiving 5 or fewer prescriptions. Additionally, when comparing patients with somatic diagnoses to patients without somatic diagnoses it produced a higher risk of potentially severe or potentially fatal PIPs (RR = 1.96, 95% CI = 1.41–2.72). These PIP with the potential to harm patients also included somatic drugs, for example: NSAIDs, antibiotics and beta-blockers. Antipsychotics were the drugs most often associated with potentially serious and potentially fatal PIP and this trend remained unchanged when analysing patients with and without somatic diagnoses separately. The prevalence of each unique PIP is low and might only appear a few times in the dataset because the number and combinations of individual medications are vast. Any analyses in which each unique PIP was excluded one by one, did not significantly alter the estimates on potential severity.

Examples of PIPs assessed to be potentially serious or potentially fatal can be seen in Table 7 and a table with the complete number of potentially fatal prescriptions has been added as Supplementary Table S1.

Discussion

Main results

Our study showed that PIP in newly admitted psychiatric patients is frequent and poses a major potential threat to

Table 5. Categories, frequency and potential clinical consequences of potentially inappropriate prescriptions (PIP).

	Total number of PIPs		Potentially non-significant		Potentially significant		Potentially serious		Potentially fatal	
Category of PIP	N	%	N	%	N	%	N	%	N	%
Interaction between drugs	125	36	2	1	42	34	49	39	32	26
Drug dosage too high	56	16	6	10	24	43	22	39	4	7
Omission of indication for treatment	46	13	26	57	11	24	8	17	1	2
Other	38	11	8	21	12	32	17	45	1	3
Interaction between drug and disease	32	9	1	2	12	38	16	50	3	9
Omission of a potentially useful medication	16	5	1	6	7	44	8	50	0	0
Inappropriate dosing interval	11	3	6	55	4	36	1	1	0	0
Drug dosage too small	8	2	0	0	6	75	1	13	1	13
Allergy	6	2	3	50	1	17	0	0	2	33
Duplicate drug	4	1	0	0	2	50	1	25	1	25
Inappropriate dosage time	3	1	1	33	2	67	0	0	0	0
Inappropriate dosage form	3	1	2	67	1	33	0	0	0	0
Inappropriate duration of treatment	1	1	0	0	1	100	0	0	0	0
Inappropriate route of administration	0	0	0	0	0	0	0	0	0	0
Total	349		56		125		123		45	

Table 6. Characteristics of patients prescribed PIPs versus those not prescribed PIPs (N = 207).

	Patients with PIP[a] N (%)	Patients with no PIP N (%)	Adjusted logistic regression analysis[b]		
			OR	95%CI	*p* value
Age (reference group: 40–59)					
18–29 years	29 (46)	34 (54)	0.66	0.30–1.44	0.296
30–39 years	26 (68)	12 (32)	1.45	0.59–3.61	0.418
40–59 years	24	49	1		
≥ 60 years	24 (73)	9 (27)	0.77	0.29–2.06	0.602
Gender (reference group: male)					
Male	54 (57)	41 (43)	1		
Female	74 (66)	38 (34)	1.44	0.75–2.76	0.273
Alcohol or substance abuse (reference group: no alcohol or substance abuse)					
No substance abuse	88 (63)	52 (37)	1		
Substance abuse	40 (60)	27 (40)	1.16	0.55–2.42	0.702
No. of prescriptions (reference group: 1–5)					
1–5 prescriptions	43 (43)	57 (57)	1		
≥ 6	85 (79)	22 (21)	3.66	1.88–7.11	<0.0001
No. of somatic diagnoses (reference group: 0)					
0 somatic diagnoses	66 (51)	63 (49)	1		
≥ 1 somatic diagnoses	62 (79)	16 (21)	2.53	1.17–5.48	<0.018
Pseudo R^2				0.15	

The reference group is the category to which all other categories are compared for each variable.
OR: odds ratio. The odds ratios reflect the association between the odds for at least one PIP and the interaction of each variable.
[a]Potentially inappropriate prescribing (PIP).
[b]Adjusted for age, gender, substance abuse, number of prescriptions and number of somatic diagnoses using logistic regression considering each patient as a cluster (N = 207).

patient safety. More than half of all patients had at least one PIP and the largest category of potentially fatal PIP was drug–drug interactions. Antipsychotics were most often associated with drug–drug interactions and potentially fatal PIP regardless of the patients' somatic health status. Too high doses of drugs along with missing indications for the use of a drug also appeared to be a substantial problem. Polypharmacy (number of prescriptions >5) and having one or more somatic diagnoses were predictive factors of PIP in general. Additionally, patients with somatic diagnoses were more often prescribed PIP with potential to harm than patients without a somatic diagnosis. Consequently, psychiatric patients with >5 prescriptions and one or more somatic diagnoses could be considered especially vulnerable from a medication safety perspective. Analysis of the impact of each unique PIP (for example a particular drug–drug interaction) showed no significant impact on the estimates and therefore supports robustness of the analysis.

Strengths and limitations

To our knowledge, this study is the first to utilize systematic medication reviews performed by clinical pharmacologists in newly admitted psychiatric inpatients. The strength of this study was the combination of the pharmacologists' clinical knowledge of psychiatric patients and pharmacological expertise. This provided a detailed evaluation of the appropriateness of the medications prescribed considering patients psychiatric as well as somatic conditions. However, each PIP was identified and assessed for potential clinical consequences by one person who might introduce a less reliable result. Ideally, each PIP should have been assessed for potential clinical consequences by two or more clinical pharmacologists and evaluated using for example a Kappa test statistic or discussed until consensus was reached. A source for reducing the precision of the estimates in this study was the fact that the assessments of severity were of potential events and not factual events.

Table 7. Descriptions of 10 potentially fatal PIPs[a] and 10 potentially serious PIPs[b].

Potential severity	Age	Sex	Medication	Intended daily dosage (unless otherwise stated)	Indication	Route of administration	Description of PIP
Potentially fatal	44	Female	Erythromycin	750 mg	Infection	Oral	Drug–drug interaction: the combination is contraindicated
			Simvastatin	40 mg	Hypercholesterolaemia	Oral	
Potentially fatal	37	Male	Ibuprofen	1800 mg	Arthritic pain	Oral	Interaction between drug and disease: the patient had previously had a brain haemorrhage and also suffered from an enzyme defect which increases the risk of haemorrhage
Potentially fatal	66	Female	Paracetamol	4000 mg daily and additionally PRN 1000 mg with no maximum dosage per day documented	Pain	Oral	Drug dosage too high
Potentially fatal	26	Male	Escitalopram	30 mg	Schizophrenia	Oral	Drug dosage too high: maximum recommended daily dosage is 20 mg
Potentially fatal	28	Female	Paliperidone	100 mg monthly	Schizophrenia	Intramuscular	Drug–drug interaction: increased risk of prolonged QT interval
			Levomepromazine	10 mg	Schizophrenia	Oral	
			Quetiapine	200 mg	Bipolar disorder	Oral	
			Lithium	30 mmol	Bipolar disorder	Oral	
Potentially fatal	34	Female	Chlorprothixene	25 mg	Schizophrenia	Oral	Drug–drug interaction: 3 antipsychotics with prolonged QTc as known side effect. No ECG or therapeutic drug monitoring provided
			Paliperidone	100 mg monthly	Schizophrenia	Intramuscular	
			Sertindole	20 mg	Schizophrenia	Oral	
Potentially fatal	22	Female	Chlorprothixene	250 mg PRN (50 mg max 5 times per day)	Schizophrenia	Oral	Drug–drug interaction: Increased risk of arrhythmia
			Risperidone	25 mg fortnightly	Schizophrenia	Intramuscular	
			Citalopram	40 mg	Schizophrenia	Oral	
Potentially fatal	26	Male	Propranolol	80 mg	Essential tremor	Oral	Interaction between drugs: increased risk of arrhythmia. No ECG was provided
			Escitalopram	30 mg	Depression	Oral	
			Abilify	30 mg	Schizophrenia	Oral	
			Olanzapine	10 mg	Schizophrenia	Oral	
			Olanzapine	(10 mg max 1 time per day)	Schizophrenia	Oral	
			Seroquel	900 mg	Schizophrenia	Oral	
Potentially fatal	38	Female	Risperidone	6 mg	Schizophrenia	Oral	Interaction between drugs: increased risk of prolonged QT interval
			Clozapine	600 mg	Schizophrenia	Oral	
Potentially fatal	75	Female	Magnesium oxide	1000 mg	Constipation	oral	Interaction between drug and disease: clinically contraindicated at eGFR values <50 mL/min per 1.73 m^2. The patients eGFR was 35 mL/min per 1.73 m^2. No serum magnesium was provided
Potentially serious	59	Female	Olanzapine	55 mg	Schizophrenia	oral	Drug dosage too high: maximum recommended daily dosage is 40 mg. Including the patient's PRN prescription daily dosage was 55 mg
Potentially serious	41	male	Methylphenidate	54 mg	ADHD	Oral	Other: contraindicated. The patient suffered depression and was psychotic
Potentially serious	79	Female	Bendroflumethiazide with potassium	1.25 + 573 mg	Hypertension	Oral	Interaction between drug and disease: may reduce serum sodium. Patients serum sodium was 133 mmol/L (Danish reference values: 137–145 mmol/L
Potentially serious	50	Female	Ibuprofen	1200 mg PRN (400 mg max 3 times per day)	Pain	Oral	Interaction between drugs: may increase serum lithium levels
			Lithium	15 mmol Li+	Bipolar	Oral	
Potentially serious	72	Female	Risperidone	25 mg every 3 weeks	Schizophrenia	Intramuscular	Interaction between drugs: increased risk of arrhythmia
			Venlafaxine	150 mg	Anxiety	Oral	
Potentially serious	44	Male	Clozapine	300 mg	Schizophrenia	Oral	Interaction between drugs: may increase level of serum clozapine (receives high dose sertraline)
			Sertraline	150 mg	Depression	Oral	

(continued)

Table 7. Continued

Potential severity	Age	Sex	Medication	Intended daily dosage (unless otherwise stated)	Indication	Route of administration	Description of PIP
Potentially serious	43	Female	Diazepam	20 mg	Anxiety	Oral	Drug dosage too high: maximum recommended daily dosage is 15 mg
Potentially serious	74	Female	Tramadol Duloxetine	100 mg 60 mg	Pain Depression	Oral Oral	Interaction between drugs: increases the risk of serotonergic symptoms. The patient is described with psychomotoric inhibition, agitation and diarrhoea
Potentially serious	42	Female	Mirtazapine	60 mg	Personality disorder	Oral	Drug dosage too high

QTc represents the heart rate corrected time taken for ventricular depolarisation and repolarisation (from the start of the Q wave to the the end of the T wave in an ECG).
PIP: potentially inappropriate prescription. The above-listed potentially fatal PIPs were chosen from the three most frequent categories represented and the potentially serious PIPs were chosen from the four most frequent categories represented. Drug–drug interactions represent the majority of PIPs as they are the most frequent category of PIP.
[a]Total number of potentially fatal PIPs was 45.
[b]Total number of potentially serious PIPs was 123.
PRN, pro re nata, a prescribed medication which is not scheduled but administered as needed.

However, assessing potential events based on available evidence is proactive in terms of medication safety.

The prescriber of identified PIP might have had rational, clinical considerations which were not documented or accessible for the clinical pharmacologists and thus complicated the assessment of severity. Our intention with this study was to initiate a debate about appropriateness of prescribing and shed light on the complexity in psychiatry as well as the attentiveness and skill needed in order to perform medication reviews. Undoubtedly, if psychiatrists, clinical pharmacologists or nurses were to discuss each PIP, disagreement would emerge. Implicit medication reviews and assessments of potential clinical consequences are complex and not necessarily reliable in every case, but have come across as the best source of estimating the magnitude of PIP.

The study only included patients whose conditions resulted in an admission to a bed unit and consequently only represents a more severely ill psychiatric population. The prescribing investigated in this study reflected the prescribing culture in Northern Denmark and cannot necessarily be generalized outside Northern Denmark. However, the results may generate hypotheses about the quality and appropriateness of prescribing in mental health care and requires new and preferably multicentre studies.

Comparisons with previous literature

It has been suggested that the presence of PIP might be a measure of the quality of prescribing in the elderly (28) and we suggest that PIP might also serve as an indicator for the quality of prescribing in psychiatric patients. Studies on the subject of inappropriate prescribing use the terms PIP and potential inappropriate medications (PIMs) interchangeably but we have chosen to consistently use the term PIP when discussing the results of this present study.

A review from 2013 reported that the prevalence of PIP in 12 observational studies using the STOPP (Screening Tool of Older Persons Prescriptions) criteria ranged from 21.4–79% (29). The STOPP criteria identify potentially inappropriate medication use in the elderly. Though this was a wide range for the prevalence of PIP, it still supported our finding of at least one PIP in 59% of the admitted patients. It was not possible, per se, to demonstrate an association between PIP and ADEs in psychiatric patients but an association between PIP and ADEs has been shown in studies with the elderly (26,30,31).

An important finding in our study was combination therapy with antipsychotics as the most frequent PIP and the most frequent potentially serious or potentially fatal drug–drug interaction when reviewing psychiatric patients' general medication profile. Combination therapy with antipsychotics has been extensively studied and is mostly recognized as a practice to be avoided (32). However, for certain categories of treatment-resistant patients, combination therapy with antipsychotics is recommendable and should always be an intentional pharmacological practice (rational psychopharmacotherapy) accompanied by close observation (32). The practice of combining antipsychotics and antidepressants has also received attention. For instance, two meta-analyses have reviewed the evidence related to treating major depressive

disorder (MDD) using combination therapy with antipsychotics and antidepressants. There was some evidence to support augmentation treatment with second-generation antipsychotics to antidepressants in MDD but the practice was also associated with a higher risk of adverse events leading to discontinuation of medication (33,34). This was, at least partly, in line with our study which indicated that drug–drug interactions involving antipsychotics and antidepressants are common and potentially a threat to patients' lives; for example due to an increased risk of cardiac arrhythmia.

This study revealed that polypharmacy and having one or more somatic diagnoses were predictive factors for PIP. This was partially in line with other studies which have also found an association between polypharmacy and PIP in the elderly (35,36). The concomitant use of several drugs is, on the other hand, a necessary and beneficial part of numerous guidelines on treating a variety of conditions. However, the higher frequency of potentially harmful PIP in patients with somatic diagnoses underlines the vulnerability and complexity of psychiatric patients in general. A recent study from the USA investigated the influence of psychiatric co-morbidities on 30-day all-cause readmissions following hospitalizations for heart failure, acute myocardial infarction and pneumonia. It was demonstrated that the rate of readmission for patients with psychiatric co-morbidity was significantly higher compared with those without a psychiatric comorbidity and that future interventions to reduce readmission should consider psychiatric aspects (37).

A literature review from 2014 on high-risk drugs suggested defining a list of high-risk drugs to improve clinically relevant patient outcomes through medication reviews (38). The suggested top twenty list encompassed all of the drugs known to have caused hospitalization, life-threatening conditions, disabilities and death due to MEs. Taking into account that we studied potentially serious or potentially fatal PIP and not factual incidences of a drug causing a serious or fatal ME, there are numerous overlaps: methotrexate, NSAID, opioids, acetylic salicylic acid, other anticoagulants, beta-blockers, antibiotics, sulphonylureas, antipsychotics and antidepressants. This indicates that drugs and drug classes considered to be high-risk drugs in general also represent a risk in psychiatric patients and must be considered when prescribing and reviewing medications.

Implications

The results of this study imply a much greater awareness towards drug–drug interactions, particularly with antipsychotics and antidepressants, is needed. Similarly, there is a need to emphasize cautious prescribing when treating patients with several drugs and somatic diagnoses. Systematic medication reviews for all patients performed by clinical pharmacologists or pharmacists may be a relevant intervention. Nevertheless, in light of the sparse resources available in most health care systems, mental health included, we need to investigate other approaches. Many of the potential problems suggested by the clinical pharmacologists and predictive factors identified in this study could be identified by nurses and therefore it might be beneficial to initiate an interprofessional approach. Nurses are the group of health care professionals that most often interact with and observe patients taking medication and thus also observe and monitor effects and side effects of medications (39). Due to these specific competencies, nurses would be a natural member of any multidisciplinary team working on improving medication safety after having received additional pharmacological and psychopharmacological training. Nurses' roles in multidisciplinary teams could possibly be to identify patients in need of systematic medication review by specialists.

Conclusion

PIP appears to be highly frequent and potentially serious in psychiatric in-patients. Most PIP was associated with psychopharmacological drugs, especially the use of antipsychotics and antidepressants. Drug–drug interactions proved to be the largest category of PIP and accounted for the largest proportion of PIP assessed to be potentially fatal. This study indicated patients receiving polypharmacy (>5 prescriptions) and patients with one or more somatic diagnoses as being potentially more vulnerable to PIP. There is an urgent need to focus on better training of physicians and nurses in order to prevent PIP. Future studies on improving medication safety should include interventions aimed at improving physicians' knowledge of pharmacology as well as nurses' knowledge and understanding of pharmacological safety issues. This would improve a rapid identification of psychiatric patients who would benefit from systematic medication reviews.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary Table 1 Potentially fatal prescriptions (n=45)

Potential severity	Age	Sex	Medication	Intended daily dosage (unless otherwise stated)	Indication	Route of administration	Description of potentially inappropriate prescription (PIP)
Potentially fatal	35	Male	Levomepromazine	300 mg PRN* (3 x 100 mg/day)	Psychosis	Oral	Drug-drug interaction: increased risk of prolonged QT interval
			Escitalopram	20 mg	Depression	Oral	
Potentially fatal	35	Male	Risperidone	37.5 mg every fortnight	Schizophrenia	Intramuscular	Drug-drug interaction: increased risk of prolonged QT interval
			Levomepromazine	300 mg PRN (3 x 100 mg/day)	Psychosis	Oral	
Potentially fatal	35	Male	Chlorprothixen	300 mg PRN (3 x 100 mg/day)	Psychosis	Oral	Drug-drug interaction: increased risk of prolonged QT interval
			Risperidone	37.5 mg every fortnight	Schizophrenia	Intramuscular	
Potentially fatal	35	Male	Chlorprothixen	300 mg PRN (3 x 100 mg/day)	Psychosis	Oral	Drug-drug interaction: increased risk of prolonged QT interval
			Escitalopram	20 mg	Depression	Oral	
Potentially fatal	35	Male	Chlorprothixen	300 mg PRN (3 x100 mg/day)	Psychosis	Oral	Drug-drug interaction: increased risk of prolonged QT interval.
			Levomepromazine	300 mg PRN (3 x 100 mg/day)	Psychosis	Oral	Chlorprothixen inhibits CYP2D6 and increases the concentration of levomepromazine in plasma
Potentially fatal	35	Male	Chlorprothixen	300 mg PRN (3 x 100 mg/day)	Psychosis	Oral	Drug-drug interaction: increased risk of prolonged QT interval.
			Risperidone	37.5 mg every fortnight	Schizophrenia	Intramuscular	Chlorprothixen inhibits CYP2D6 and increases the concentration of risperidone in plasma
Potentially fatal	35	Male	Escitalopram	20 mg	Depression	Oral	Drug-drug interaction: increased risk of prolonged QT interval. Escitalopram inhibits CYP2D6 and increases the concentration of risperidone in plasma
			Risperidone	37.5 mg every fortnight	Schizophrenia	Intramuscular	
Potentially fatal	35	Male	Escitalopram	20 mg	Depression	Oral	Drug-drug interaction: increased risk of prolonged QT interval. Escitalopram inhibits CYP2D6 and increases the concentration of levomepromazine in plasma
			Levomepromazine	300 mg PRN (3 x100 mg/day)	Psychosis	Oral	

Potentially fatal	43	Male	Clopidogrel	75 mg	Prevention of thrombosis	Oral	Drug-drug interaction: increased risk of hemorrhage
			Naproxen	500 mg	Pain	Oral	
			Venlafaxine	300 mg	Depression	Oral	
Potentially fatal	35	Male	Clozapine	350 mg	Schizophrenia	Oral	Drug-drug interaction: increased risk of prolonged QT interval
			Venlafaxine	300 mg	Depression	Oral	
			Quetiapine	150 mg PRN (3 x 50 mg/day)	Schizophrenia	Oral	
Potentially fatal	41	Female	Quetiapine	50 mg	Mood disorder	Oral	Drug-drug interaction: increased risk of prolonged QT interval
			Litarex	12 mmol	Mood stabilizing	Oral	
			Aripiprazol	20 mg	Mood disorder	Oral	
Potentially fatal	60	Female	Seroquel	150 mg	Depression	Oral	Drug-drug interaction: increased risk of prolonged QT interval
			Risperidone	1 mg	Mental disorder	Oral	
			Nortriptyline	450 mg	Mental disorder	Oral	
			Citalopram	40 mg	Depression	Oral	
Potentially fatal	28	Female	Paliperidon	100 mg monthly	Schizophrenia	Intramuscular	Drug-drug interaction: increased risk of prolonged QT interval
			Levomepromazine	10 mg	Schizophrenia	Oral	
			Quetiapin	200 mg	Bipolar disorder	Oral	
			Lithium	30 mmol	Bipolar disorder	Oral	
Potentially fatal	22	Female	Chlorprothixen	250 mg PRN (5 x 50 mg/day)	Schizophrenia	Oral	Drug-drug interaction: Increased risk of arrhythmia
			Risperidone	25 mg fortnightly	Schizophrenia	Intramuscular	
			Citalopram	40 mg	Schizophrenia	Oral	
Potentially fatal	66	Female	Chlorprothixen	250 mg PRN (5 x 50 mg/day)	Uncertain	Oral	Drug-drug interaction: Increased risk of arrhythmia
			Quetiapine	100 mg (4 x 25 mg/day)	Anxiety	Oral	
			Venlafaxine	225 mg	Depression	Oral	
Potentially fatal	34	Female	Chlorprothixen	25 mg	Schizophrenia	Oral	Drug-drug interaction: 3 antipsychotics with prolonged QTc as known side effect. No ECG or therapeutic drug monitoring provided.
			Paliperidon	100 mg monthly	Schizophrenia	Intramuscular	
			Sertindol	20 mg	Schizophrenia	Oral	
Potentially fatal	38	Female	Risperidone	6 mg	Schizophrenia	Oral	Drug-drug interaction: increased risk of prolonged QT interval
			Clozapine	600 mg	Schizophrenia	Oral	

Potentially fatal	85	Female	Sertraline	100 mg	Anxiety	Oral	Drug-drug interaction : increases the risk of hemorrhage
			Acetylsalicylic acid	75 mg	Anticoagulant	Oral	
			Clopidogrel	75 mg	Prevention of thrombosis	Oral	
Potentially fatal	38	Female	Risperidone	6 mg	Schizophrenia	Oral	Drug-drug interaction: increased risk of prolonged QT interval
			Clozapine	600 mg	Schizophrenia	Oral	
Potentially fatal	66	Male	Clozapine	20 mg	Schizophrenia	Oral	Drug-drug interaction: increased risk of prolonged QT interval. No ECG was provided.
			Citalopram	300 mg	Depression	Oral	
Potentially fatal	69	Female	Levomepromazine	40 mg	Anxiety	Oral	Drug-drug interaction: increased risk of arrhythmia
			Chlorprothixen	45 mg	Agitation	Oral	
			Quetiapine	400 mg PRN (4 x 100mg/day)	Mental disorder	Oral	
Potentially fatal	26	Male	Propranolol	80 mg	Essential tremor	Oral	Drug-drug interaction: increased risk of arrhythmia. No ECG was provided.
			Escitalopram	30 mg	Depression	Oral	
			Abilify	30 mg	Schizophrenia	Oral	
			Olanzapin	10 mg	Schizophrenia	Oral	
			Olanzapin	10 mg PRN (1 x 10 mg/day)	Schizophrenia	Oral	
			Seroquel	900 mg	Schizophrenia	Oral	
Potentially fatal	41	Male	Chlorprothixen	100 mg	Mental disorder	Oral	Drug-drug interaction: Prescribed moderate/high dosage of chlor-prothixen which inhibits the metabolism of risperidone
			Risperidone	37.5 mg every fortnight	Anxiety/depression	Intramuscular	
Potentially fatal	44	Female	Erythromycin	750 mg	Infection	Oral	Drug-drug interaction: the combination is contraindicated
			Simvastatin	40 mg	Hypercholesterolaemia	Oral	
Potentially fatal	44	Female	Erythromycin	750 mg	Infection	Oral	Drug-drug interaction: the combination is contraindicated
			Paliperidon	9 mg	Schizophrenia	Oral	
Potentially fatal	44	Female	Erythromycin	750 mg	Infection	Oral	Drug-drug interaction: increased risk of prolonged QT interval.
			Chlorprothixen	200 mg PRN (4 x 50 mg/day)	Mental disorder	Oral	

Potentially fatal	36	Male	Imipramine	10 mg	Depression	Oral	Drug-drug interaction: increased risk of prolonged QT interval
			Venlafaxine	300 mg	Depression	Oral	
			Risperidone	0.5 mg PRN (1 x 0.5 mg/day)	Mental disorder	Oral	
			Promethazine	25 mg	Sleep problems	Oral	
Potentially fatal	41	Male	Risperidone	37.5 mg every fortnight	Mental disorder	Intramuscular	Drug-drug interaction: increased risk of prolonged QT interval.
			Chlorprothixen	100 mg PRN (2 x50 mg/day)	Mental disorder	Oral	
Potentially fatal	42	Female	Ziprasidon	160 mg	Depression	Oral	Drug-drug interaction: increased risk of prolonged QT interval.
			Chlorprothixen	200 mg PRN (4 x 50 mg/day)	Anxiety	Oral	
Potentially fatal	50	Female	Risperidone	3 mg	Mental disorder	Oral	Drug-drug interaction: increased risk of arrhythmia
			Escitalopram	30 mg	Depression	Oral	
Potentially fatal	44	Male	Levomepromazine	25 mg	Sedation	Oral	Drug-drug interaction: increased risk of prolonged QT interval. Chlorprothixen is a high dose. Previous AMI.
			Chlorprothixen	75 mg	Anxiety	Oral	
Potentially fatal	57	Female	Quetiapine	50 mg	Mental disorder	Oral	Drug-drug interaction: increased risk of arrhythmia
			Chlorprothixen	75 mg PRN (3 x 25 mg/day)	Anxiety	Oral	
			Lithium	24 mmol	Bipolar disorder	Oral	
			Nortriptyline	75 mg	Depression	Oral	
Potentially fatal	47	Male	Paracetamol	4000 mg daily and additionally PRN 1000 mg without a maximum dosage per day documented	Pain	Oral	Drug dosage too high: No maximum dose recorded
Potentially fatal	64	Female	Escitalopram	30 mg	Depression	Oral	Dosage too high: No maximum dose recorded
Potentially fatal	61	Male	Paracetamol	4000 mg daily and additionally PRN 1000 mg without a maximum dosage per day documented	Pain	Oral	Dosage too high: No maximum dose given
Potentially fatal	26	Male	Escitalopram	30 mg	Depression	Oral	Drug dosage too high: maximum recommended daily dosage is 20 mg
Potentially fatal	56	Female	Zuclopenthixole	100 mg PRN (1 x 100mg/day)	Sedation	Oral	Omission of indication for treatment: all medications were prescribed PRN and all medications were prescribed in moderate to high doses.
			Olanzapine	20 mg PRN (2 x 10 mg/day)	Mental disorder	Oral	
			Quetiapine	400mg PRN (4 x 100 mg/day)	Mental disorder	Oral	

Potentially fatal	68	Female	Chlorprothixen	45 mg	Anxiety	Oral	Other: Contraindicated when hypokaliaemic. The patients serum potassium was 3,1 mmol/l (Danish reference values: 3,6-4,6 mmol/L)
Potentially fatal	37	Male	Ibuprofen	1800 mg	Arthritic pain	Oral	Interaction between drug and disease: the patient had previously had a brain hemorrhage and also suffered from an enzyme defect which increases the risk of hemorrhage
Potentially fatal	75	Female	Magnesium oxide	1000 mg	Constipation	Oral	Interaction between drug and disease: clinically contraindicated at [$]eGFR values <50 ml/min per 1.73m^2. The patients eGFR was 35 ml/min per 1.73m^2. No serum magnesium was provided
Potentially fatal	48	Female	Ibuprofen	600 mg	Pain	Oral	Interaction between drug and disease: The patient had previously suffered a deep vein thrombosis
Potentially fatal	43	Female	Amlodipine	5 mg	Hypertension	Oral	Drug dosage too small: Hypertension insufficiently treated. Patient's blood pressure was 171/97 mmHg
Potentially fatal	53	Male	Venlafaxin	150 mg	Depression	Oral	Allergy: Type 2-3 response described in the electronic patient record but not recorded in the [§]EMR.
Potentially fatal	42	Female	Pregabalin	[%]N/A	N/A	N/A	Allergy: swelling of the tongue described in the electronic patient record. Not listed as CAVE in the EMR
Potentially fatal	42	Female	Ibuprofen Diclofenac	400 mg PRN (1 x 400 mg/day) 100 mg PRN (2 x50 mg/day)	Pain Pain	Oral Oral	Duplicate drug: increased risk of gastrointestinal bleeding

* PRN (pro re nata): a prescribed medication which is not scheduled but administered as needed

[$]eGFR: estimated glomerular filtration rate

[%]N/A: not applicable

[§]EMR: Electronic Medication Record.

–CAVE: used in medicine to indicate medications the patient should avoid – usually due to abnormal reactions.

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-033-3

AALBORG UNIVERSITY PRESS